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BLOOD

Iron Metabolism • Anemias • Leukocytes • Immunohematology Blood Clotting and Anticoagulants

Studies of Absorption of Iron from the Gastrointestinal Tract. *William J. Grace and Ronald K. Doig.** Department of Medicine, New York Hospital-Cornell Medical Center, New York City.

The absorption of iron from the gastrointestinal tract has been studied by means of the iron tolerance curve. Observations were made on 34 patients with hypochromic anemia, 31 patients with normochromic anemia; and 50 experiments on 7 healthy persons were performed.

The results indicate that half of the patients with hypochromic anemia absorbed little or no iron compared to the healthy subjects. Patients with normochromic anemia absorbed optimal amounts of iron. The data indicate that failure to absorb iron may be an important contributing mechanism in states of iron deficiency.

Twenty-six observations have been made on a subject with a gastric fistula, and in these observations all the iron placed in the stomach entered the small intestine. In these experiments there was no relationship between absorption and gastric acidity. Absorption was optimal on days of good spirits and relaxation, and below optimal on days of conflict and indecision.

The Absorption of Food Iron and Inorganic Iron by Normal, Iron-Deficient, and Hemochromatotic Subjects. *Robert B. Chodos, Joseph F. Ross, Leonard Apt,* James Halkett,* and Myron Pollycove,** with the technical assistance of Mary Pratt, and Joan Donovan. The Radioisotope Unit and Medical Service, Veterans Administration Hospital, Boston.

Although iron deficiency is one of the commonest nutritional deficiencies afflicting the human race, little is known concerning the capacity of the human organism to absorb the iron present in foodstuffs.

Radioactive tracer methods have been employed to investigate the absorption of food and inorganic iron by normal subjects, iron-deficient patients, and patients with hemochromatosis before and following treatment with venesection. Eighty-five such studies have been performed. Radioactive iron has been incorporated into food (eggs, meat, vegetable greens) as metabolically-bound iron by employing biologic methods (administration of radioactive iron to chickens; nutriculture of plants in radioactive iron containing solutions). These labelled foodstuffs were fed to human subjects, and quantitative determinations made of the amount of radioactive iron retained in the body and the amount incorporated into hemoglobin. Our observations indicate that food iron is absorbed much less readily than inorganic iron and that the simultaneous administration of certain foodstuffs (e.g., egg) with inorganic iron markedly decreases absorption of inorganic iron. Absorption of food iron was negligible in normal subjects. More food iron was absorbed by iron-deficient subjects, but considerably less than with inorganic iron. Untreated hemochromatotic subjects absorbed little inorganic iron and even less food iron. After many venesections, patients with hemochromatosis absorbed considerably more iron.

These studies indicate that food iron is absorbed much less efficiently by human subjects than is inorganic iron. However, food iron absorption is increased in hemochromatosis after venesections, and this suggests that iron stores will reaccumulate unless venesections are continued or absorption limited.

* An asterisk indicates "by invitation."

Erythropoietic Serum Factor in Rabbits with Turpentine-Induced Inflammations. *A. J. Erslev and P. H. Lavietes.** Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut.

Acute and chronic inflammations are usually associated with a slight to moderate anemia caused by a decrease in erythropoietic activity. None of the known metabolic alterations which take place during inflammation have so far been shown to induce such a bone marrow depression.

Recently red cell production has been found to be stimulated and probably regulated by a serum factor, the "anemic" factor. In order to investigate the possible role of this factor in the pathogenesis of the anemia of inflammation it was decided: (1) to estimate the amount of "anemic" factor present in serum of rabbits with a turpentine-induced inflammation after a standardized bleeding and (2) to evaluate the response of rabbits with a turpentine-induced inflammation to serum containing a known amount of "anemic" factor.

One ml. of turpentine was injected i.m. to rabbits which subsequently were made anemic by bleeding. Two hundred ml. of serum obtained from these rabbits 48 hours later was injected into each of 7 normal rabbits. The mean reticulocyte response of these rabbits to the serum was found to be significantly lower than the response found in 7 control rabbits receiving "anemic" serum from donors which were made anemic in the same way but did not receive an injection of turpentine (P between 0.05 and 0.01).

In the second experiment 7 rabbits were given an injection of turpentine before they received 200 ml. of serum from healthy but anemic donors. The mean reticulocyte response was significantly lower than the response of the above mentioned control group (P between 0.05 and 0.01).

These experiments suggest that an inflammatory reaction either interferes with the production of "anemic" factor and its action on the bone marrow, or that it removes "anemic" factor from the blood stream, preventing it from reaching the bone marrow.

Anemia of Thermal Injury. Studies of Radioiron Utilization and of Erythrocyte Life Span in Rats. *William M. Davis** *and Edward L. Alpen** (introduced by *W. James Kuhl, Jr.*). Division of Biological and Medical Sciences, U. S. Naval Radiological Defense Laboratory, San Francisco.

The anemia of thermal injury has been investigated in rats recovering from high intensity radiant energy thermal burns of approximately 25% of total body area. We are reporting both measurements of utilization of tracer doses of radioiron (Fe^{59}) and measurements of mean erythrocyte life span, utilizing Fe^{59} by the iron loading technic of Burwell, in both control and burned rats. Mean erythrocyte life span was determined as the time interval from initial incorporation of 50% of maximal uptake to the loss of 50% of incorporated Fe^{59}.

Utilization of Fe^{59} in burned rats was more rapid and the level of incorporation higher than in simultaneously studied control animals. The mean erythrocyte life span of control rats was 51 ± 5 days and of burned rats 27 ± 4 days. The burned rats showed early and continuing random destruction of erythrocytes at a rate greater than normal. This is in contrast to control rats in whom significant degrees of random destruction did not occur until after 30 days. These findings are interpreted as showing an active hemolytic process in rats recovering from thermal burns. This hemolytic process is compensated for in young rats by increased rates of medullary and extramedullary hematopoiesis. This increased red cell production is indicated by the reticulocytosis, accelerated uptake of Fe^{59}, and the return of the circulating red cell volume to normal.

The Mechanism of the Anemia Associated with Rheumatoid Arthritis. *E. J. Freireich,** *J. F. Ross, T. B. Bayles, C. P. Emerson, S. C. Finch,* with the technical assistance of *Miss C. MacDonald.* Massachusetts Memorial Hospitals and the Robert Breck Brigham Hospital, Boston.

Active rheumatoid arthritis commonly is associated with a moderate anemia refractory to antianemic therapy. We have studied: (1) red blood cell production, utilizing radioactive iron tracer techniques, (2) red blood cell destruction by fecal urobilinogen measurements and (3) red cell survival with the Ashby technic of differential agglutination.

1. An injected tracer dose of radioiron was rapidly removed from the plasma of these patients. The serum iron concentration, however, was depressed so that the calculated total iron turnover rate was within the normal range. External monitoring over major body organs showed that the largest fraction of radioiron cleared from the plasma was deposited in the bone marrow and subsequently discharged into the blood. Eighty to 95% of the injected radioiron was utilized for red cell formation in 7 to 10 days. Thus, the rate of red cell formation was within the normal range.

2. The quantity of hemoglobin destroyed per day, as calculated from fecal urobilinogen measurements, was within the normal range.

3. Normal donor cells transfused into rheumatoid arthritis patients showed a decrease in their effective life-span. In contrast, red cells from rheumatoid arthritis patients transfused into normal recipients survived normally. Thus, these patients produced a red cell capable of normal survival, but have an extracorpuscular hemolytic system unassociated with any identifiable immune mechanism which is responsible for a decrease in the life-span of their red cells.

Although these patients had a normal rate of

erythropoiesis, the shortened red cell survival resulted in a decreased red cell mass. The reasons for a failure of the marrow to increase its rate of red blood cell production under these circumstances are discussed.

The Nature of the Anemia of Rheumatoid Arthritis. *Franklin G. Ebaugh, Jr., Ralph E. Peterson* and Joseph J. Bunim.* National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda, Maryland.

The nature of the anemia in rheumatoid arthritis is at present poorly understood. The purpose of this study was to evaluate the relative importance of increased hemolysis versus deficient red cell production (bone marrow failure) as a cause of the anemia by means of red cell survival and iron metabolism studies. In the series of patients studied, the serum iron ranged from 32 to 80 gamma %, serum copper from 123 to 175 gamma %, and total serum iron binding capacity from 285 to 370 gamma %. Red cell survival was measured by Ashby selective agglutination and autotransfused radioactive sodium chromate 51-tagged erythrocytes. The mean cell life of the red blood cell ranged between 70 and 100 days (normal 120 days). The fraction of the red cell mass destroyed each day ranged between 1.0 to 1.4% (normal: 0.83%) or from 1.2 to 1.7 times normal. Comparison of the rate of red blood cell production per day with the expected normal rate of production (0.24 ml. of packed RBC per Kg. body weight) revealed rates ranging from 0.88 to 1.3 times normal. The above results have been correlated with results obtained by radioactive Fe^{59} plasma clearance and RBC uptake. It is concluded that both an increase of hemolysis and a failure of the bone marrow to respond in a normal fashion are factors contributing to the anemia of arthritis. The degree to which each of these two processes was responsible for the anemia varied from patient to patient.

Erythrocyte Fragilities in Plumbism. *John W. Harris and Mortimer S. Greenberg.** The Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School, Boston.

Aub et al described changes in red cell fragilities in plumbism in 1925. These changes were restudied by present-day methods in 10 patients with chronic lead poisoning and anemia. Elevated urine lead and coproporphyrin III levels were present in all patients.

Under standard conditions, the osmotic fragility (OF) and mechanical fragility (MF) of patients' red cells were measured on fresh venous blood and on blood subsequent to sterile incubation for 24 hours at 37°C. The effect of $PbCl_2$ upon normal human erythrocytes in vitro was also studied.

The OF of 10 patients' fresh red cells was normal or slightly decreased. However, after 24 hours incubation, a portion of the red cells became more resistant to lysis in hypotonic saline. This is in contrast to the decreased resistance of all normal erythrocytes after incubation. The MF of fresh blood was normal (<3.4%) or slightly elevated. After 24 hours incubation, the average MF for 9 of these patients was 20.0 ± 4.6% as compared with 10.6 ± 3.5% for 31 normals. Three patients were treated with calcium ethylenediaminetetraacetate and, in these, the hemoglobin levels rose and the OF and MF values of incubated blood reverted towards normal.

Changes in OF and MF similar to those described were noted when normal human red cells, suspended in serum or saline, were incubated with $PbCl_2$ in vitro.

The observed abnormalities of the erythrocytes of patients with lead poisoning can be produced in normal red cells in vitro and may be related to the increased rate of red cell breakdown in such patients.

Absorption and Excretion of Crystallin Vitamin B_{12} When Applied to the Nasal Mucosa. *Raymond W. Monto and James T. Howell.** Division of Hematology, Henry Ford Hospital, Detroit.

Recent reports as to the effectiveness in pernicious anemia of the administration by inhalation or nasal installation of vitamin B_{12} suggest that contact with intrinsic factor is not a prerequisite for the absorption of vitamin B_{12} through the respiratory mucous membrane. In view of these observations it is pertinent to determine the B_{12} activity in the urine utilizing this mode of application.

It has been established that normal subjects and pernicious anemia patients excrete vitamin B_{12} in the urine in similar quantities following parenteral injection. Two normal subjects were given nasal installations of 200, 100 and 50 μg. of crystalline vitamin B_{12} in 0.5 ml. saline each on separate days. Urine specimens were collected before and at 2, 5 and 8 hours after administration of the drug and assayed for total vitamin B_{12} activity by use of the test organism *Lactobacillus leichmanii*. The urinary B_{12} activity following intranasal instillation of the vitamin suggests similar patterns, but in smaller quantities than noted after parenteral administration of equal amounts.

Glass has studied a glandular mucoprotein derived from gastric mucin. He has shown this substance to be absent in patients with pernicious anemia and to potentiate the hematopoietic activity of vitamin B_{12} when taken orally.

The nasal mucosa normally produced about 1 L. of mucous daily which is swept to the nasopharynx and swallowed. To evaluate the possibility that intranasal B_{12} might exert its hematopoietic action by means of interreaction with mucin within the nose, a nasal washing experiment was undertaken. One hundred μg. of crystalline B_{12} in 0.5 ml. saline

was administered to the nasal mucosa of a normal subject. After a 20-minute interval the nasal passages were washed with 200 ml. of saline. This solution was then introduced via stomach tube to a pernicious anemia patient in relapse. Reticulocytosis did not occur in a 14-day test period. This patient later demonstrated a reticulocytosis of 44.3% when 150 mg. of crystalline B_{12} were applied directly to the mucous membrane of the nasal turbinate bone.

The urinary B_{12} activity following intranasal administration of the vitamin to 2 normal and patients with pernicious anemia in relapse suggests similar patterns to those noted after parenteral administration. A single attempt to demonstrate intranasal binding of B_{12} with nasal mucous was unsuccessful. Crystalline B_{12} in saline solution and as crystals is rapidly absorbed and excreted by the kidneys when applied to the nasal mucosa.

Urinary Excretion of Orally Administered Co^{60}-labeled Vitamin B_{12} in Normal Subjects and Patients with Pernicious Anemia and Sprue. *Edward H. Reisner, Jr., Charles Rosenblum* and Mary C. Morgan.** New York City.

Schilling demonstrated that if 1 mg. of vitamin B_{12} is given parenterally to subjects who have ingested 2 μg. of Co^{60}-labeled B_{12}, significant amounts of the labeled vitamin can be recovered from the urine in the subsequent 24 hours. Using this technic we have recovered in normal subjects from 8 to 20% of the ingested dose. With the injection given 2 hours before the labeled B_{12} from 7 to 11% was recovered, while if 6 hours elapsed before it, from 1.5 to 7% was recovered. This suggests that high blood levels of B_{12} do not prevent absorption of the vitamin but do influence the amount retained in the body.

Pernicious anemia patients showed no excretion of the labeled B_{12} unless the oral dose was accompanied by a source of intrinsic factor. Several different concentrates of intrinsic factor were tested for activity in this manner and showed urinary B_{12} excretions of from 0.6 to 4.3% of the ingested dose, depending upon the preparation used. There was a qualitative correlation between the Schilling test on a particular preparation and its clinical behavior in treated patients in relapse. The same intrinsic factor preparations showed considerable variation of absorption in different patients with pernicious anemia in remission, as well as on repeated trials in the same patient.

Some sprue patients showed no absorption of the labeled vitamin B_{12}, by this test, even when it was accompanied by intrinsic factor. This, therefore, may offer a method of distinguishing between the sprue patient with achlorhydria and the patient with pernicious anemia, and diarrhea.

When folic acid was substituted for intrinsic factor no significant radioactivity was present in the urine.

Folic Acid Metabolism in the Anemia of Hepatic Cirrhosis. *James H. Jandl* and Arnold A. Lear** (introduced by *William B. Castle*). The Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School, Boston.

Nutrients required in hematopoiesis were evaluated in 16 patients with chronic alcoholism, hepatic cirrhosis and macrocytic anemia. Serum Vitamin B_{12} levels were normal in all patients. Ascorbic acid was absent from the venous blood buffy coat in 11 patients, one of whom manifested clinical scurvy. In 12 patients pteroylglutamic acid (PGA) and citrovorum factor (CF) produced no hematologic responses and were promptly excreted in the urine. Four patients with severe anemia, megaloblastic bone marrow, and free gastric hydrochloric acid developed characteristic hematologic responses to folic acid preparations. Two patients responded to daily intramuscular doses of 250 and 500 μg, respectively, of PGA. Two responded to an oral yeast preparation containing in each daily dose 150 μg of "free" and 1350 μg of conjugated folic acid. After incubation with chick pancreas conjugase, the same amount of yeast, containing 1500 μg of folic acid activity, was administered daily; no further reticulocyte response and no rise in urinary excretion of folic acid or CF occurred. A subsequent daily oral dose of 1500 μg of PGA produced no additional hematologic response but led to an abrupt rise in urinary folic acid activity. Those patients responding hematologically to folic acid did not have uniformly poor diets. Since the absorption of naturally-occurring folic acid and the utilization of PGA, as indicated by hematologic responses, appeared to be undisturbed, these observations suggest that the requirement for folic acid may be increased in certain patients with cirrhosis.

Postnatal Hematologic Pattern of Erythroblastosis Fetalis. *Jane F. Desforges and Liam G. O'Connell.** Rh Laboratory and Pediatric Service, Boston City Hospital, Boston (aided by a grant from the Charlton Research Fund, Tufts Medical School, and by a research grant (A-556) from the National Institutes of Health, Public Health Service.)

Serial hematologic observations over 2 to 12 month periods are presented on 33 cases of erythroblastosis fetalis.

In the 26 babies who received replacement transfusions, average values for the pretransfusion period were hemoglobin 13.3 Gm.%, reticulocytes 5%, and leukocytes 17,000. Antibodies, bilirubin, hemoglobin, reticulocytes and white count showed no apparent correlation.

Following immediate post-transfusion drop, the reticulocyte curve rose during the first 3 days, then fell below 1%. The dimensions of the curve were

independent of pre- or post-treatment hemoglobin values.

After transfusion the minimal hemoglobin level averaged 7.5 Gm.% and was associated with a second reticulocytosis. The time at which this minimal level occurred correlated with the second day post-transfusion hemoglobin value and was unrelated to other parameters.

The reappearance of antibody in 14 babies did not affect the hemoglobin or reticulocyte curve.

Pretransfusion blood was similar to normal cord blood in limits, modes and width of osmotic fragility curves. Increased mechanical fragility was noted in some pretreatment specimens, but was unrelated to other laboratory studies. Post-treatment findings simulated adult blood, some variation occurring during the period of minimal hemoglobin value.

Untransfused babies followed a similar pattern except that the time of minimal hemoglobin level was unrelated to second day values. Osmotic fragility curves showed no striking changes, but mechanical fragility was abnormal.

Conclusion: Replacement transfusion modifies reticulocyte and hemoglobin curves but does not destroy the underlying postnatal pattern.

Abnormal erythrocyte fragility may occur in both groups.

Separation of Hemoglobin C From Hemoglobin C Trait Blood by Electrophoresis Convection. *L. M. Kraus* and D. B. Morrison** (introduced by *Alfred P. Kraus*). Department of Medical Laboratories, Clinical Chemistry, College of Medicine, University of Tennessee, Memphis. (Supported in part by the Herbert Herff Foundation, Memphis.)

The separation of individual hemoglobins from naturally occurring mixtures of hemoglobins has been investigated using electrophoresis convection.

Hemoglobin solutions were fractionated in the electrophoresis convection apparatus of S. Raymond using 0.06 M barbiturate buffer pH 8.65, 6°C., 20 volts and 0.3 amperes. The type and purity of the hemoglobin solution in the upper reservoir and in the combined middle and lower reservoirs was determined by paper electrophoresis and electrophoresis in the Klett Tiselius apparatus using 0.06 M barbiturate buffer pH 8.6. The hemoglobin solution of patient 1 (approximately 72% C and 28% A) separated, yielding a highly purified hemoglobin C in the upper reservoir after electrophoresis convection for 16 hours. The hemoglobin solution of patient 2 (approximately 75% C and 25% A) separated, yielding a highly purified hemoglobin C in the upper reservoir after electrophoresis convection for 11 hours. Hemoglobin C with a small contamination of hemoglobin A was found in the upper reservoir after electrophoresis convection for 6 hours of the combined middle and lower reservoirs. The mobility and the electrophoretic patterns of the hemoglobin C from the upper reservoir were the same as that of a known hemoglobin C.

Further studies of the separation of the hemoglobins found in blood from sickle cell trait and sickle cell-hemoglobin C disease patients, as well as other hemoglobin combinations, are in progress.

It has been possible to separate a highly purified hemoglobin C fraction from the blood of 2 patients having hemoglobin C trait by electrophoresis convection.

Erythrocyte Destruction in Sickle Cell Anemia: Simultaneous N^{15}-Hemin and N^{15}-Stercobilin Studies. *G. Watson James, III and Lynn D. Abbott, Jr.** Laboratory for Clinical Investigation, Department of Medicine and Department of Biochemistry, Medical College of Virginia, Richmond.

A study of erythrocyte survival in sickle cell anemia was made by isotope analysis of hemin and stercobilin labeled with heavy nitrogen.

An adult Negro male with sickle cell anemia in a steady state (hemoglobin 5.9 Gm./100 ml., reticulocytes 22.8%) was given orally 2 500 mg. doses of N^{15}-glycine (31 atom % N^{15}) 3 hours apart. His erythrocytes during the first four days were labeled in the nitrogen of heme with a "tag" about 10 times that found in normal subjects given the same quantity of N^{15}-glycine. Hemin isolated at 5–7 day intervals and analyzed for N^{15} afforded a method of studying the survival of his erythrocytes. Stercobilin was isolated from each consecutive stool for 60 days and was analyzed for N^{15}.

The hemin N^{15} and stercobilin N^{15} concentrations and disappearance studies were nearly identical. This is in contrast to previous N^{15}-stercobilin studies in normal or pathologic conditions. The source of stercobilin here was practically entirely from indiscriminate random destruction of the circulating erythrocytes, which had no definite life span. The hemoglobin turnover rate was much greater than that found by London and associates from N^{15}-hemin studies in sickle cell anemia patients with much less severe anemia. The half-life of the circulating erythrocytes calculated from our N^{15}-stercobilin and N^{15}-hemin data was only about 14 days, which would indicate a mean survival time of 20 days with a turnover rate of 5% per day. This is about 6 times that found in the normal individual.

Renal Function in Long Standing Sickle Cell Disease. *J. Leonard Brandt.* Department of Medicine, State University of New York, College of Medicine at New York, Brooklyn.

Previous work from this laboratory has demonstrated marked renal vasoconstriction following infusions of pooled hemoglobin solution to normal persons; similarly, we have shown that renal ischemia develops promptly with the induction of a hemolytic episode in a subject with paroxysmal cold hemo-

globinuria. It has seemed of importance to investigate the renal functional patterns in a group of subjects known to have had frequent hemolytic crises over a long period of time, and in whom chronic hemosiderinuria is known to occur. In nine subjects with sickle cell disease, ranging in age from 10 to 38 years, measurements of glomerular filtration rate (C_I), renal plasma flow (C_{PAH}), TM_{PAH}, filtration fraction, and ratio C_{PAH}/TM_{PAH} were made. All subjects had a hemoglobin of at least 10 Gm. at the time of study. None were studied during crisis.

The GFR in the group studied averaged 125.2 cc. per minute (range 80–170); RPF averaged 801 cc. per minute (range 500–975); TM_{PAH} averaged 96.0 mg. per minute (range 61.8–151.0); filtration fraction averaged 16% (range 11.5%–19.4%); the ratio C_{PAH}/TM_{PAH} averaged 8.2 (range 6.2–10.3).

Although a small number of cases have been studied, the data indicate the likelihood of there being a lowered renal resistance in the sickle cell kidney and an increased tubular mass. These data might explain the ability of the kidneys of patients with various hemolytic diseases to withstand repeated hemolytic crises.

The Pathologic Physiology of Hematopoiesis and Iron Metabolism in Chronic Myelogenous Leukemia Before and After Radiophosphorus Therapy. *Myron Pollycove,* Leonard Apt* and Joseph Ross,* with the technical assistance of *M. A. Pratt and J. M. Donovan.* Radioisotope Unit, VA Hospital, Boston, Mass.

Tracer doses of plasma protein-bound Fe^{59} were given intravenously to normal individuals and to patients with chronic myelogenous leukemia.

Prior to Fe^{59} injection, plasma and red cell volumes were determined by the simultaneous use of Evans Blue dye and P^{32}-labelled erythrocytes. Employing gamma ray counting technics, the removal time (in hours) of Fe^{59} from the plasma, the turnover rate (in mg. per 24 hours) of plasma iron and the incorporation of iron (in %) into erythrocytes were determined. The anatomic distribution of Fe^{59} in various body tissues of special significance in erythropoiesis and iron metabolism was measured simultaneously by external body survey with a mobile scintillation detector.

Patterns of the kinetics of iron metabolism and erythropoiesis determined in the patients with chronic myelogenous leukemia were found to differ markedly and significantly from the normal. Erythropoiesis occurred at relatively high levels in the spleen and liver and at a low level in the bone marrow. Although the turnover of iron in the plasma was greater than normal, the fraction of this iron which was subsequently incorporated into the hemoglobin of circulating erythrocytes was low (65–78%). These functional abnormalities were correlated with chemical and morphologic changes in the peripheral blood, feces, bone marrow, and spleen.

The studies after P^{32} therapy indicated that the rise in hemoglobin and erythrocyte values was due principally to an improvement in bone marrow function.

These studies demonstrate the importance of the spleen in erythropoiesis in patients with chronic myelogenous leukemia and that the hematologic improvement following P^{32} therapy results principally from increased erythropoiesis in the bone marrow.

Relationship of Body Hematocrit to Venous Hematocrit in Polycythemia and Leukemia. *S. P. Masouredis and Jorge Soni.** Donner Laboratory, University of California, Berkeley, California.

The development of methods for independent and simultaneous determination of the dilution volume of red cells and plasma has suggested that the proportion of RBC to plasma in the peripheral venous blood is greater than that found throughout the body by about 10%. The theoretic significance for fundamental cardiovascular physiology and its practical importance in the clinical determination of blood volume warrant a critical re-evaluation of this problem.

RBC volume was determined with P^{32}-labelled cells (G-M tube), and plasma volume with I^{131} human serum albumin (scintillation counter) in 40 patients. Intravenous injections were made with a 1 ml. mercury-calibrated tuberculin syringe, and the I^{131} HSA was administered 30 minutes after the P^{32}-labelled RBC.

The results were critically examined for the following sources of systematic error: inadequate mixing, nonprotein-bound I^{131}, free P^{32} in injection mixture and in plasma of samples, and initial rate of loss of I^{131} HSA from the plasma. The plasma volume was obtained by extrapolation of I^{131} plasma activity on semilog paper, and the RBC mass from whole blood P^{32} and the true hematocrit was determined from (I^{131} per ml. whole blood)/(I^{131} per ml. plasma). Blood volume was calculated as plasma volume + red cell mass, and body hematocrit from (RBC mass)/(RBC mass + plasma volume). The body hematocrit agreed with the true venous hematocrit within the estimated experimental error, 5–6%. Failure to correct the data for the systematic errors enumerated above yields a venous hematocrit 10–15% higher than the body hematocrit.

Studies of Leukocyte Alkaline Phosphatase Determined by a Clinically Applicable Histochemical Method. *Harold Brodell* and Scott N. Swisher.* Department of Medicine, University of Rochester School of Medicine and Dentistry, Rochester, New York.

Valentine and collaborators have shown that high values of leukocyte alkaline phosphatase are

found in patients with polycythemia vera, neutrophilia and leukemoid responses, whereas low values are found in chronic myelocytic leukemia. Biochemical estimation of leukocyte alkaline phosphatase is relatively difficult and is not practical for clinical use.

The Gomori phosphatase staining technic as described by Wachstein has been applied to smears of leukocytes obtained by differential centrifugation. A method of semiquantitation of enzyme activity has been developed based upon microscopic grading from 0–4 + of the depth of staining of 100 successive leukocytes. A "leukocyte alkaline phosphatase index" has been derived from these data. Phase-contrast microscopy has been found useful in examining these preparations.

Leukocyte alkaline phosphatase indices and chemical determinations have been compared in 11 normal subjects and 28 patients with a variety of granulocytic abnormalities. Leukocyte alkaline phosphatase indices have been determined on 20 additional normal subjects and 25 similar patients. Normal leukocyte alkaline phosphatase indices range from 60 to 185 with a mean of 140. There is good general agreement between the results of the biochemical and histochemical technics. The normal range of phosphatase index is relatively wider than the range for chemical estimation. However, low and high values of phosphatase index are clearly separated.

The diagnostic value of the histochemical leukocyte alkaline phosphatase technic, applicable to routine clinical use, is best illustrated in a group of 9 patients involving the differential diagnosis of myeloid metaplasia or chronic myelocytic leukemia.

Interference of Ethionine with Synthesis of Antihemophilic Globulin. *Judith G. Pool* and Theodore H. Spaet.* Department of Medicine, Stanford University School of Medicine, San Francisco.

Pancreatic necrosis was produced in male Slonaker rats by means of ethionine, (250 mg./day), and the effect on blood coagulation factors studied.

Apparently this strain of rats is particularly resistant to the effects of ethionine, as the majority of the animals survived for 1 to 2 weeks on daily injections of a dose described as lethal to other strains after a single injection. However, by about 7 days after initiation of ethionine injections, these animals showed considerable weight loss, developed marked alopecia, showed bile-stained, matted abdominal hair, and usually had several dried blood-covered injuries on the feet. Assay of the plasma showed a drop of antihemophilic globulin to less than 10% of normal. There was, in addition, a marked fall in prothrombin, labile accelerator, and stable accelerator, and some decrease in fibrinogen. Tissue sections showed loss of acinar structure, secretory granules, and basophilia in the pancreas, as well as some inflammatory reaction, but by no means complete fibrosis and destruction. The liver presented localized necrotic degeneration of cells around the central veins, general increase in acidophilia and some pericapillary edema. The bone marrow became hypoplastic and some cells exhibited vacuolization. Testis showed considerable damage, thymus some involution, and kidney acidophilia, but gut, spleen and muscle were relatively unaffected. Electrophoretic analysis of the serum of these animals showed marked reduction of the α-globulins, decrease in the β-globulin, and little or no effect on the γ-globulin or albumin.

It is concluded that ethionine interferes with the synthesis of antihemophilic globulin and other clotting factors. The data indicate that this is not due to a generalized effect on all protein synthesis.

The Plasma Responsiveness Test in Antihemophilic Globulin Deficiency. *Martin C. Rosenthal.* Department of Hematology and Medicine, Mount Sinai Hospital, New York City.

It is generally agreed that fresh plasma is the most effective systemic measure in hemophilic bleeding. The recommended amount of such plasma has varied from as little as 50 ml. to over 250 ml. In order to: (a) gain a reasonable approximation of an individual patient's optimal plasma requirement and (b) ascertain that proportion of plasma that might benefit the majority of hemophiliacs, an in vitro plasma responsiveness test was utilized.

The test consisted of apportioning into 3 test tubes, precalibrated at the 2.1 ml. mark, 0.1 ml., 0.05 ml., and 0.01 ml., of freshly drawn normal plasma. Using silicone technic, blood was drawn from the hemophilic subjects, placed into each tube to the mark, mixed, and incubated at 37°C. The coagulation time and 1 hour serum prothrombin time were noted for each tube. A standard coagulation time was performed simultaneously.

Eighteen subjects, identified as patients lacking antihemophilic globulin were studied. Standard coagulation times ranged from 15 to 79 minutes (average: 45 minutes, normal: under ten minutes). Serum prothrombin activities ranged from 11.0 to 14.8 seconds (average: 12.5 sec., normal: over 21 seconds).

When 0.1 ml. of normal plasma was added to 2 ml. of hemophilic blood, the coagulation time in 16 of the 18 subjects was reduced to the expected normal of 10 minutes or less. The 2 subjects who showed negligible reduction proved to be refractory to large amounts of plasma both in vitro and in vivo. In contrast to the effect on the coagulation time was the serum prothrombin activity. Eight of the 18 cases still remained under the normal value of 21 seconds. These cases tended to be among those with more prolonged standard coagulation times.

Reduction of the added normal plasma to 0.05 ml. resulted in restoration of the coagulation time to

normal in 10 of 18 cases, but serum prothrombin activity was now abnormal in 12 of 18.

Further reduction to 0.01 ml. gave only 5 normal coagulation times and 1 normal serum prothrombin activity.

Assuming a hematocrit of 40, the addition of 8% of normal plasma to hemophilic plasma will restore the coagulation time to normal in all except refractory cases. In 50% of the cases, this amount will also result in normal prothrombin consumption. Any lesser amount will prove ineffective with rare exceptions. Based on the expected plasma volume of a patient, these data may be applied in computing approximate plasma requirements.

Studies on a Circulating Anticoagulant Active Against the Antihemophilic Factor, Found in a Hemophilia Carrier. *Theodore H. Spaet and Beverly G. Kinsell.** Stanford University School of Medicine, San Francisco.

Coagulation studies were performed on a female hemophilia carrier who presented a history of hemorrhagic manifestations since childhood. The patient's blood showed a prolonged clotting time and reduced prothrombin consumption, but prothrombin, both prothrombin conversion accelerators, platelets, and fibrinogen were normal. Addition of 20% of the patient's plasma to normal plasma caused prolongation of the recalcified clotting time, and more than 25% of normal blood was required to improve the patient's prothrombin consumption. The patient's plasma failed to improve prothrombin consumption in known hemophiliacs, but was normally active against PTC-deficient blood. Concentrated fraction I of Cohn restored the patient's prothrombin consumption to normal, but in amounts considerably greater than were needed for hemophiliacs. No excessive antithrombin, or activity against tissue thromboplastin were demonstrable. Although sheep and rabbit plasma were relatively inactive against the patient's clotting defect, plasmas of hog, beef, and rat were as effective as with hemophiliacs.

The findings indicate that: (1) the patient had a circulating anticoagulant, (2) this anticoagulant was specific against AHF, (3) the anticoagulant had different activity against the AHF of different species.

The data provide evidence that the antihemophilic factor is species specific.

On the Forssman-like Behavior of Cold Hemagglutinins. *Chris J. D. Zarafonetis and Virginia F. Colville.** Department of Medicine, Hematology Section Temple University School of Medicine, Philadelphia.

Attention has recently been called to the phenomenon of cold hemagglutination of sheep erythrocytes as a factor in false-positive heterophile agglutination tests for infectious mononucleosis. The present study was undertaken to determine whether or not cold hemagglutinins behave as Forssman antibodies in absorption tests.

Accordingly, sera obtained from a wide variety of clinical material were tested for the presence of cold agglutinins for (a) sheep erythrocytes and/or (b) human erythrocytes (usually type "O"). Specimens containing cold agglutinins for either sheep or human RBC were then subjected to absorption with guinea-pig kidney suspension or with boiled beef erythrocytes after the method of Davidsohn. Both unabsorbed and absorbed specimens from a given patient were tested simultaneously against the same RBC suspension in order to eliminate the factor of agglutination variability of cells from different sheep or different human donors.

Cold agglutinins for sheep RBC were regularly removed by absorption with guinea-pig kidney suspension, but were little affected by absorption with boiled beef RBC. Similar results were also obtained with most of the sera which contained cold agglutinins for human RBC. Exceptions were noted, however, in tests on sera from a patient with acquired hemolytic anemia, and another with lupus erythematosus.

These results indicate that most cold hemagglutinins behave as Forssman antibodies. While cold agglutinins for sheep RBC may be removed by absorption with guinea-pig kidney suspension, the agglutination may also be dispelled by warming to 37°C. In the interests of economy and simplicity, it is recommended that the latter procedure be followed in routine heterophile agglutination tests.

A Case of Autoimmune Hemolytic Disease in a Dog. *Gerald Miller, Scott N. Swisher, and Lawrence E. Young.* Departments of Pediatrics and Medicine, University of Rochester School of Medicine and Dentistry, Rochester, New York.

A case of naturally-occurring autoimmune hemolytic disease accompanied by severe anemia and spherocytosis (acquired hemolytic anemia) has been studied in a young cocker spaniel, a household pet. To our knowledge there are no other previously reported instances of the occurrence of this type of hemolytic anemia in any species other than man. Current widespread interest in immunohematologic disorders, and the failure of numerous efforts to produce the disease experimentally, prompted the extensive studies which have been made in the present case. The hematologic and serologic manifestations of the canine disorder are remarkably similar to those observed in the comparable human hemolytic disease.

As in the human disorder, the affected dog's erythrocytes are agglutinable by antiglobulin serum (anti-dog-serum rabbit serum). An agglutinin has been eluted from the erythrocyte stroma which reacts serologically like the autoagglutinin in the dog's serum. These substances, presumably plasma globulins, act as panagglutinins for dog erythrocytes. The

rate of red cell destruction has been estimated and the beneficial effect of ACTH therapy observed.

It can be concluded that the autoimmune hemolytic disease frequently encountered in man is not confined to the human species. More widespread effort directed to the detection of "naturally occurring" hemolytic disease in other species may provide sufficient experimental material to expedite certain types of observations. Studies of the comparative pathology should help elucidate the etiology and pathogenesis of this disorder.

Effects of Sonic Energy on Blood Coagulation in Vitro. *Sylvia L. Axelrod** (introduced by *Frederick S. Bigelow*). The Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School, Boston.

An attempt to obtain cell-free platelet extracts prompted the utilization of focused sound waves in the ultrasonic range. Vibrations of 420 kc./sec. effected virtually complete platelet lysis in 60 seconds. Saline extracts of sonically lysed platelets are far more effective in accelerating the clotting of platelet-poor normal plasma than are equivalent physiologic concentrations of intact washed platelets. Prolonged exposure to sonic energy does not alter the accelerator, antiheparin, or vasoconstrictor components of platelets. Intact platelets are essential for clot retraction, and, as predictable, brief sonic treatment destroys this property. Normal and hemophilic platelets were compared in these studies, and no differences between them were discernible. However, the coagulation of hemophilic plasma is not significantly altered by addition of lysed platelets in physiologic quantity.

While sonic energy is not detrimental to platelet extracts or fractions, commercial thromboplastin so treated suffers prompt and progressive deterioration. Plasma, subjected to sonic energy, manifests defective thrombin formation and SPCA generation, and is deficient in labile factor and antihemophilic activity. Thrombin formation in such plasma can be rectified by lysed or intact platelets but not by commercial thromboplastin. Thus, differences between active platelet materials and commercial thromboplastin are emphasized. Prothrombin, thrombin, and preformed SPCA are not measurably affected by sonic treatment, and the effect on fibrinogen is erratic.

These studies demonstrate that sonic energy effects rapid and efficient platelet lysis without injury to platelet constituents. Its effects on other coagulation factors may offer new approaches to the study of coagulation.

"Thrombocytopenia of Replacement Transfusion": A Cause of Surgical Bleeding. *Mario Stefanini, Irma B. Mednicoff,** *Lucy Salomon** *and Edmund W. Campbell.* Blood Research Laboratory, New England Center Hospital and Tufts College Medical School, Boston. (Aided by grants-in-aid from the National Institutes of Health, the American Heart Association and the Atomic Energy Commission.)

Severe bleeding was encountered in 13 patients undergoing surgery who received large volumes of bank blood (10–15 pints or more) to replace blood loss at operation. A study revealed multiple deficiencies of the hemostatic mechanism in these patients. Fibrinolysis with fibrinogenopenia was observed in 2 cases. More commonly, however, laboratory findings indicated platelet deficiency. Platelet count was low, clot retraction and prothrombin consumption impaired, bleeding time prolonged and capillary fragility increased. It is postulated that platelets lost through bleeding were not replaced with the administration of bank blood. This contains only few or no platelets, which are destroyed by the effects of vacuum and contact with glass surfaces. In 10 of 11 cases prompt control of excessive bleeding followed administration of platelet concentrates or repeated transfusions of blood collected by gravity in plastic bags or silicone-coated bottles, which are known to preserve platelets.

The complication described is infrequent and, perhaps, occurring only in patients with potential deficit of platelet production (liver disease, bone marrow depression, etc.). It appears important, nevertheless, to administer blood collected in nonwettable containers or, at least, obtained by gravity and with careful and prompt mixing with the anticoagulant solution to patients given several blood transfusions during surgery. These technics are effective in preventing excessive loss of platelets and may reduce the incidence of the complication described.

The Effects of Compounds E and F, ACTH, and Splenectomy, in Idiopathic Thrombocytopenic Purpura. *William A. Steiger, Chris J. D. Zarafonetis and Sarah K. Cary.** Temple University Medical School, Philadelphia.

Ten consecutive patients were treated with Compounds E and F, ACTH, and splenectomy, for idiopathic thrombocytopenic purpura. Several patients have been treated with alternating courses of these agents in order to compare their effectiveness. There appears to be no correlation between the platelet response to steroid therapy and that to splenectomy. The steroid therapy resulted uniformly in decreased bleeding and diminished capillary fragility. The platelet response was variable, with 5 of 10 patients having platelet rises to normal values following steroid or ACTH therapy.

Two of the patients exhibited positive Coombs' Tests and positive serologic tests for syphilis with negative *Treponema* and immobilization tests. The presence of an altered immune mechanism in ITP is indirectly confirmed.

The variable course of ITP is illustrated and the therapeutic conclusions are outlined. We feel that the use of Compounds E and F, and ACTH now constitutes conservative therapy—as opposed to watchful waiting which, we believe, is now radical—in view of the possibility of bleeding into vital areas.

Species Differences in Influence of Sequesterene (EDTA) on Prothrombin Assay Methods. *E. P. Cronkite and G. J. Jacobs.** Naval Medical Research Institute, Bethesda, Maryland.

The disodium salt of ethylene diamine tetraacetic acid (EDTA) has become an effective anticoagulant in preparation in separated platelets and leukocytes. Since the use of EDTA might become more general, it appeared most desirable to study its influence on prothrombin assay systems in diverse species.

The influence on the 2-stage prothrombin assay method of Ware and Seegers and the 1-stage method of Quick was investigated.

The results with the 2-stage assay using 0.050 M and 0.025 M EDTA and comparing the results to the assay with 0.14 M sodium citrate as an anticoagulant showed marked species differences. The difference varied from 92% of the citrate value in man to 7% in monkeys using 0.050 M EDTA and from 95% in man and dog to 33% in monkeys using 0.025 M EDTA. Other species fell between these ranges. In every case, 0.050 M EDTA decreased the prothrombin yield as compared to citrate.

When the concentration of EDTA in dog plasma was decreased, the yield of prothrombin increased to a maximum at 0.020–0.025 M EDTA. Below this concentration spontaneous coagulation occurred. This increase in yield occurred with a constant pH and was not related to Ca^{++} concentration in the reaction mixture.

After defibrination of 0.05 M EDTA plasma with thrombin as in the first step of the 2 stage system, there is a rapid decrease in prothrombin yield with incubation at room temperature. After 5 hours no prothrombin can be detected. With 0.025 M EDTA and 0.14 M sodium citrate, there is no appreciable decrease over the same time interval. Human plasma shows a similar phenomenon but at a slower rate.

When 0.050 M EDTA defibrinated plasma is incubated for 5 hours and then dialyzed against 0.14 M citrate defibrinated plasma by a continuous flow system for 24 hours an interesting sequence of events occurs. During incubation the prothrombin yield diminishes to nearly zero. After dialysis is commenced the yield of prothrombin increases and by the end of 24 hours is approximately back to the original values.

In the 1-stage prothrombin system, the prothrombin time was longer with EDTA than with citrate in all species tested. These results appeared independent of Ca^{++} concentration. However, increased Ca^{++} concentration altered the end point so that it was difficult to determine the precise coagulation time.

These preliminary studies indicate that EDTA at specific concentrations has a peculiar effect on the coagulation components, aside from chelating Ca^{++}. The site of action is presumably prothrombin, and dialysis against citrate reverses the effect.

The Proconvertin Test: A Simplified Method and its Application to the Study of Anticoagulant Processes and Body Fluids. *Dionysius Adamis,** *Herbert S. Sise and Delbert Kimball.** Boston City Hospital, Boston.

Owren showed that by passage of beef plasma through 20% asbestos filter pads in a Seitz filter there was almost complete removal of proconvertin and only partial removal of prothrombin. Using this proconvertin-free plasma as a reagent, he assayed for proconvertin by mixing a dilution of the test material with the filtered plasma and then measuring the clotting time with thromboplastin and calcium. This method was extensively studied by us and it was found that the preparation of the reagent by Seitz filtration was time consuming and unpredictable. There was great variation with different plasmas, different filter pads, and different makes of filter pads. A simpler reproducible method consists of multiple filtration of an aliquot of plasma repeatedly through the same layer of powdered wood charcoal, whereby more complete separation can be achieved with less loss of prothrombin. This can be easily used in any laboratory. A reagent could be prepared with loss of only 25–35% of the prothrombin and yet a Quick prothrombin time up to 18 minutes. A purified preparation of prothrombin from this material showed practically no conversion to thrombin in 10 minutes when incubated with thromboplastin and calcium, unless preparations containing both Ac-globulin and proconvertin were added.

In 100 cases it was found that the early phase of phenylindanedine administration for anticoagulant purposes was characterized by a low proconvertin relative to prothrombin. The later phase, however, was characterized by the reverse. It was noted that in the latter phase, particularly in those who had received the drug for many months, there is the best evidence of a true anticoagulant effect as evidenced by prolongation of glass clotting time and prevention of clot formation in blood flowing through foreign lumen.

In 1 individual with congenital deficiency of proconvertin, a transient small rise in proconvertin could be demonstrated after administration of vitamin K_1.

The demonstration of proconvertin in small amounts in abnormal serous effusions and spinal fluid was made.

Activation of a Plasma Proteolytic Enzyme by Trypsin and Streptokinase. *Irving Innerfield and Alfred Angrist.** Mt. Sinai Hospital and Jewish Memorial Hospital, New York City.

The addition of suitable quantities of streptokinase or crystalline trypsin to plasma in vitro activates a potent proteolytic enzyme. Aliquots of an SK-plasma mixture on lycine ethyl ester showed hydrolysis in excess of either SK or plasma alone. Using a l-arginine methyl ester substrate and ferric hydroxamic acid as the indicator aliquots of a trypsin-plasma mixture also showed hydrolysis in excess of either trypsin or plasma.

Following the production of acute inflammation in the rabbit's eye (4 drops of 15% mustard oil in a mineral oil base) 8 rabbits were given 5,000 units SK in ½ cc. human plasma i.v. or i.m.; 8 rabbits were given 1 mg. trypsin in ½ cc. human plasma i.v. or i.m.; 8 rabbits served as controls. A marked anti-inflammatory response, characterized by prompt subsidence of edema and conjuncitival injection occurred in the treated animals. Panophthalmitis and total blindness developed in 5 of the 8 controls.

Intramuscular Trypsin in the Treatment of Thrombophlebitis. *Martin M. Fisher and Nathan D. Wilensky.* Peripheral Vascular and Medical Services of the Kings County Division of Kings County Hospital, Brooklyn.

We have treated 80 patients with thrombophlebitis with intramuscular trypsin. In those with acute thrombophlebitis, relief of pain, calf tenderness and swelling was noted, as well as a decrease of the elevated temperature and sedimentation rate. The results have been uniformly good in 75 of the 80 patients. In many cases, relief was noted in the first 12 hours after treatment was instituted. In acute thrombophlebitis, if improvement was not noted after the 4 days with trypsin alone, the treatment was discontinued and evaluated as unsuccessful. In the chronic cases of thrombophlebitis, the results have not been as effective as in the acute cases. The palpable thrombus was slower to resolve than the acute inflammation. The regime of therapy was usually 2.5 mg. of trypsin i.m. once or twice daily for 1 to 4 days, depending upon the clinical response.

In most cases of acute thrombophlebitis, the symptoms and signs of acute inflammation subsided in a direct relationship to the first intramuscular injection of trypsin. There has been a low incidence of pulmonary emboli; in no case have they been fatal. Postphlebitic syndrome has been rare.

Intramuscular trypsin is no substitute for anticoagulants, as it has no anticoagulant action. It is easy to administer compared to the intravenous route. Intramuscular trypsin has a definite tendency to shorten the course of acute thrombophlebitis.

CARDIOVASCULAR SYSTEM

Heart • Heart Failure • Circulatory Dynamics Peripheral Vessels

Valvular Congenital Pulmonic Stenosis: Preoperative Studies of 8 Patients with 5 Postoperative Physiologic Studies. *Robert L. Grissom, Louis A. Selverstone, Luke Pascale and Angelo P. Creticos.** Department of Medicine of the Presbyterian Hospital and the University of Illinois, College of Medicine. (Aided by a grant from the United States Public Health Service.)

Congenital valvular pulmonic stenosis is ideally suited for correction by surgical incision. Despite the very small size of the aperture in 8 patients (by preoperative calculations all less than 0.5 cm.) the adjustment by adolescents and young adults was sufficient for ordinary and, in some cases, vigorous activity. The striking findings by physiologic studies, including catheterization, exceeded the functional disability. An effort was made to determine if controlled bicycle exercise would accentuate these differences. The only significant variable was a rise in right ventricular pressure and no abnormal rise in right atrial pressure was observed. Preoperative pulmonic valve resistances were calculated and found to be high.

Postoperative catheterization studies were repeated in 5 out of 8 surgical patients. A marked decrease in right ventricle to pulmonic artery pressure gradient was seen in only 1 of the 5. One patient with moderate postoperative decrease in pressure failed to show any further fall in a second postoperative study several months later. In 1 patient, an infundibular pressure chamber was initially overlooked in the preoperative catheterization studies and was not detected by the surgeon at operation but noted distinctly in the postoperative tracing. A moderate fall in his right ventricular pressure was noted postoperatively. Calculation of the orifice opening by the Gorlin equation for pulmonary stenosis disclosed an enlarged orifice in the distal valvular stenosis but very little change in the proximal subvalvular stenosis. There was no over-all significant change in cardiac output.

Diagnosis of Tricuspid Insufficiency: Clinical Features in 60 Cases with Associated Mitral Valve Disease. *Daniel S. Lukas and Gonzalo Sepulveda.** Department of Medicine, New York

Hospital-Cornell Medical Center, New York, N. Y. (Aided by a grant from the New York Hospital-Cornell Medical Center Research Fund.)

Of 146 patients with rheumatic heart disease and predominant mitral valve involvement studied by the technic of cardiac catheterization, 60 were found to have a right atrial pressure curve characteristic of tricuspid insufficiency. The clinical diagnosis of tricuspid insufficiency had previously been made in only 23.3% of the cases. All the patients who had cardiac failure were under optimum medical control at the time of the study.

The most constant clinical features were auricular fibrillation (present in 58), persistent liver enlargement, a history of right ventricular failure and roentgenographic evidence of moderate to severe enlargement of the right atrium. A small QRS complex, frequently of the rsr′ pattern, in V_1 of the electrocardiogram was found in 60.4% of the cases.

The pulmonary vascular resistance, right atrial mean and right ventricular pressures were distinctly greater as compared to a group of patients with auricular fibrillation and a similar degree of mitral involvement but without tricuspid insufficiency.

The classical clinical features of tricuspid insufficiency, that is, venous and hepatic pulsations, and ascites, were not frequently observed, and were seen more often in patients with right atrial mean pressures greater than 10 mm. Hg.

Tricuspid insufficiency, functional or organic, is a frequent complicating lesion in mitral valvular disease and its diagnosis should be suspected in any case with auricular fibrillation, persistent liver enlargement and definite increase in size of the right atrium.

Comparison of Physiologic Studies in 17 Patients with Mitral Stenosis before and after Operation. *Robert L. Grissom, Luke Paskale, Angelo P. Creticos* and Louis A. Selverstone.* Department of Medicine of the Presbyterian Hospital and the University of Illinois, College of Medicine. (Aided by a grant from the United States Public Health Service.)

Pressure-flow calculations serve to make a satisfactory estimate of preoperative mitral valve orifice opening but make a poor correlation with the known surgical opening in the postoperative state, as noted in valve size calculations on 17 patients. Effect of myocardial disease, hypertrophy, associated valvular disease and pulmonary arteriolar constriction are persistent factors in the postoperative state that perpetuate the preoperative pressure-flow relationship. No measurable factor obtained by catheterization correlated well with the high degree of improvement seen in the postoperative patients studied. As shown by electrocardiogram, only one of 17 showed a significant reduction in right ventricular hypertrophy postoperatively. All patients preoperatively showed evidence of right ventricular hypertrophy and, by catheterization, a mean pulmonary arterial pressure at least twice normal at rest. Postoperatively, significant fall in pressure in pulmonary artery was seen in less than half of the patients and did not correlate with the degree of improvement. Calculation of pulmonary arteriolar resistance postoperatively showed a scattering of improvement. Comparison of preoperative and postoperative x-ray studies showed more than 10% reduction in some, but this factor also showed scatter. Other variables, pulmonary capillary wedge pressure, pulmonary arteriolar resistance and heart work, are compared in resting and exercise state before and after operation.

The Hemodynamic Effects of Acute Digitalization in Mitral Stenosis. *Daniel S. Lukas and Jorge Araujo.* Department of Medicine, New York Hospital-Cornell Medical Center, New York City. (Aided by a grant from the New York Hospital-Cornell Medical Center Research Fund.)

The effects of digitalization on the circulation in 6 patients with mitral stenosis and severe pulmonary symptoms but without right ventricular failure were investigated by the technic of cardiac catheterization. Normal sinus rhythm was present in 5 patients; atrial fibrillation with a slow ventricular rate in 1. During a period of 1 hour following administration of 0.8 mg. of ouabaine via the catheter no significant change occurred in the markedly elevated pulmonary "capillary," pulmonary arterial and right ventricular pressures or in the low cardiac output. The patient with fibrillation and a very small mitral orifice (surgical confirmation) had an unusual hemodynamic pattern with almost normal pulmonary vascular pressures and a very low cardiac output which was also unmodified by ouabaine.

The lack of response to rapid digitalization contrasts with the changes that occur after ouabaine in patients with left ventricular failure or myocarditis. It is concluded that the modifications of the pulmonary circulation and the pulmonary symptoms related thereto in mitral stenosis are primarily due to the mechanical effects of the valvular lesion rather than to myocardial failure. The lack of change in cardiac output after digitalization lends further support to the concept that the output in mitral stenosis is depressed by some unknown mechanism in order to prevent elevation of the resting pulmonary "capillary" pressure above plasma protein osmotic levels.

The Effects of Aortic Valvular Disease on Left Ventricular Function. *Richard Gorlin, Michael B. Matthews,* Raymond Daley,* Ian K. R. McMillan* and W. E. Medd, Jr.** Department of Cardiology, St. Thomas' Hospital, London; Medical Clinic, Peter Bent Brigham Hospital and Harvard Medical School, Boston.

Nine patients with aortic stenosis (AS), 10 with stenosis and insufficiency (AS-AI) and 5 with insufficiency (AI) were studied at rest by cardiac catheterization. Eighteen exercise and 9 atropine observations were made. Fick cardiac outputs, pulmonary capillary (PC) and systemic arterial pressures were measured. In 3 patients, total left ventricular (LV) stroke work, and in the others only effective stroke work could be estimated.

Effective stroke work was normal in 11 of 19 patients with AS and AS-AI and 4 of 5 with AI. Resting PC, an index of LV diastolic pressure, was 16 mm. Hg or less (upper normal = 12) in 16 of 22. On effort, effective stroke work was fixed or fell in 11 of 14 with AS-AI and in only 2 of 5 with AI, although PC rose in every patient.

Nearly normal resting filling pressures, despite increased total LV stroke work, seemed related to LV hypertrophy and to postulated servo-adjustment to maximal work output. Because atropine cardioacceleration did not increase PC while simple leg elevation did, PC rise on effort was considered related to mobilization of blood to pulmonary circuit behind a ventricle with fixed ability to do work. The fact that, in AS and AS-AI, stroke work was fixed maximally at rest and did not change with PC increase was correlated with the fact that hydraulic relationships in tight stenosis permitted little increases in valve flow and hence in stroke output beyond a certain limit, despite large increases in valve pressure gradient. Consequently, there resulted a flat stroke work-filling pressure (Starling) curve.

Ballistocardiographic Changes Obtained during Attacks of Angina Pectoris. *Raymond Penneys.* Vascular Section, Robinette Foundation, Hospital of the University of Pennsylvania, Philadelphia.

Ballistocardiograms (Starr type) and electrocardiograms were taken before and during attacks of angina pectoris in 3 patients. Before attacks, the electrocardiograms and ballistocardiograms were essentially normal. During each attack studied, the electrocardiograms were unchanged but the ballistocardiograms showed strikingly significant changes. In 1 patient the ballistocardiogram changed from completely normal to completely abnormal when angina was induced by ciagarette smoking or by exercise. Another patient was studied during a spontaneous attack of angina while resting on the ballistocardiographic table. The record changed dramatically, the slightly abnormal complexes replaced by a series of phasic waves with no normal complexes identifiable. In the third patient angina was brought on by the "induced anoxemia" method by lowering the arterial oxygen saturation to 78% as measured by the oximeter (Circulation *1:* 415, *4:* 190). The ballistocardiogram, which had been somewhat abnormal while breathing air, became grossly abnormal, with several different types of bizarre ballistic complexes appearing. It is concluded that ballistocardiograms taken during attacks of angina pectoris may help establish objectively the diagnosis of coronary artery disease in some instances when the electrocardiogram fails.

Relationship of Adrenalin and T Wave Inversion in the Anxiety State. *Alvin P. Shapiro and Jere H. Mitchell.** Department of Internal Medicine, Southwestern Medical School of The University of Texas, Dallas.

Although transient inversion of the T wave has been frequently observed in patients with anxiety, the mechanism of this change has not been established. In an effort to elucidate this problem further, detailed electrocardiographic studies were done in a patient with an acute anxiety state and in 3 normal controls.

A 23-year-old female presented symptoms mimicking myocardial infarction and displayed T wave inversion in all leads. There were no accompanying signs of cardiac disease and the T waves reverted to normal following reassurance and sedation. Using a continuous recording technic, it was noted that the T waves could be inverted by many stimuli provoking anxiety, such as discussion of heart disease or of venipuncture, actual venipuncture, and attachment to a face mask. Inhalation of 100% oxygen and administration of nitroglycerine did not prevent the inversion. Administration of adrenalin produced T wave inversion identical to that noted with anxiety-provoking stimuli, even when the adrenalin was given without the patient's knowledge and in amounts too small to be subjectively detected. Saline, administered without the patient's knowledge, produced no change, but when it was given with the suggestion that it was adrenalin, inversion occurred. Similar small doses of adrenalin and similar attempts to provoke anxiety in 3 control patients failed to produce T wave change.

The study offers two conclusions: (1) The T wave changes appeared to be a consequence of endogenous adrenalin, evoked by anxiety and (2) myocardial hypersensitivity to adrenalin must exist, inasmuch as amounts too small to produce symptoms in the patient with anxiety, nevertheless elicited T wave inversion, while failing to affect the controls. This hypersensitivity may itself be related to the anxiety state.

Antifibrillatory Effect of Prostigmine in Experimental Hypothermia. *A. V. Montgomery,** *Arthur E. Prevedel** *and Henry Swan.* Departments of Physiology and Surgery, University of Colorado School of Medicine, Denver.

The use of hypothermia to permit periods of circulatory arrest is becoming more common in cardiovascular surgery. However, the high incidence

of ventricular fibrillation during hypothermia has been discouraging. The present report is concerned with the antifibrillatory effect of prostigmine. In the control series 23 dogs were cooled to 25°C. during hyperventilation. In these animals, ventriculotomy uniformly (100%) caused ventricular fibrillation which could not be permanently converted by the electric defibrillator. In 15 animals prostigmine 1–4000 (.05 ml./Kg.) was given intravenously or intra-auricularly. Ventriculotomy induced fibrillation in only 7 of these animals (47%). Electric defibrillation was attempted in 5 of the latter and was successful in each instance. When prostigmine 1-4000 was given by coronary perfusion immediately after circulatory arrest in a dose sufficient to reduce the heart rate to 25–10 beats per minute, (usually from 1 to 3 ml.) all 16 dogs survived a ventriculotomy without fibrillation (0%). Open catheterization of the coronary sinus in hypothermic dogs caused ventricular fibrillation in 10 of 11 animals. Ten animals protected by coronary perfusion of prostigmine underwent similar catheterization without fibrillation. Continuous coronary perfusion of acetylcholine also prevents fibrillation during ventriculotomy, which suggests that the antifibrillatory effect of prostigmine might be due to an accumulation of acetylcholine. However, preliminary experiments indicate that atropine does not consistently negate the antifibrillatory effect of prostigmine or acetylcholine.

Thiamine and Cocarboxylase Concentration in Heart, Liver and Kidney of Patients with Heart Failure. *Michael G. Wohl,* Martin Brody,* Charles R. Shuman and Richard Turner.** Nutrition Project, Philadelphia General Hospital and Temple University School of Medicine, Philadelphia.

It has previously been shown that patients with long standing heart failure have several biochemical evidences of thiamine deficiency. Among the causes for this deficiency, the administration of mercurials has been shown to increase the rate of urinary excretion of the vitamin. In the present study, the tissue thiamine and cocarboxylase contents were measured in patients with congestive heart failure because of evidence showing that the heart muscle of thiamine deficient experimental animals has a decreased ability to oxidize pyruvate.

Heart, liver and kidney tissues were obtained at autopsy from 9 patients with congestive heart failure and from 7 noncardiac control cases. The thiamine and cocarboxylase contents were determined in wet tissues as well as per gram of nitrogen of the tissues. The methods employed for free thiamine content was that of Hochberg and Melnick, and for total thiamine that of Hochberg, Melnick and Oser. Cocarboxylase was represented as the difference between total and free thiamine.

This study disclosed that all the tissues of the cardiac patients had a lower concentration to total thiamine and cocarboxylase than those of the noncardiac group. The differences were statistically significant for heart muscle. In liver tissues the difference was significant for thiamine alone. Although the kidney tissue from cardiac cases showed lower values than the controls, the differences were not statistically significant. This investigation provides further evidence of thiamine deficiency in patients with chronic refractory cardiac decompensation. Whether the thiamine content of the heart muscle was sufficiently reduced to impair oxidative metabolism in these cases is a subject for further study.

Thiamine Deficiency in Patients with Chronic Cardiac Decompensation. *O. H. Wood* and J. M. Evans.* Department of Medicine, The George Washington University Medical School, Washington, D. C.

Factors of dietary restriction and selection, as well as hepatic insufficiency and impaired intestinal absorption could contribute to thiamine deficiency in patients under treatment for chronic cardiac decompensation. To appraise this matter 13 subjects with cardiac edema were studied using the pyruvic acid tolerance test (Williams and associates, Arch. Int. Med., 1943.) Serial observations (2 to 7 per subject) were conducted in 9 of the 13 subjects in the presence of varying amounts of edema as oral vitamin B complex was administered. A control group of 16 subjects included 9 with compensated heart disease, 3 apparently healthy laboratory personnel and 4 subjects with miscellaneous disorders without apparent nutritional components.

When initially studied the pyruvic acid was elevated in 11 of the 13 heart failure subjects; dietary intake was considered adequate in only 1 of the 13. Of the 9 subjects serially studied, as oral vitamin B complex was administered, in 7 pyruvic acid fell to normal and remained so even with increasing decompensation. Of the 16 control subjects, 3 exhibited elevated pyruvic acid levels. Dietary intake had been normal in 2 of the 3 patients.

It would appear that thiamine deficiency is a frequent finding in patients with chronic cardiac edema. The success of orally administered thiamine in correcting the deficiency suggests that impaired intestinal absorption is not a critical factor. In most of the subjects intake of vitamin B was inadequate by appraisal of the dietary history.

Blood Volume Determination by Radiochromium Tagged Red Cells: Comparative Studies of Normal and Congestive Heart Failure Patients. *Wm. A. Reilly,* R. M. French,* F. Y. K. Lau,* K. G. Scott* and W. E. White** (introduced by *Paul M. Aggeler*). Medical Service and the Radioisotope Unit, Ft. Miley V.A. Hospital, San Francisco.

For the determination of whole blood volume, tagging of red cells with Cr^{51} has these advantages: Cr^{51} stays fixed in the cells for long periods (days), the radiation dose is low (0.01 rads), and its measurement is done simply with scintillation counting.

5–10 cc. of whole blood is seeded with Cr^{51} 20000 c.s. (as $Na_2Cr^{51}O_4$); plasma is discarded; saline is added to approximately the original volume (5 to 10 cc.) and this is reinjected into the patient. Mixing is complete after 10 to 15 minutes in the normals and after 20 to 30 minutes in decompensated cardiacs.

89 normals had a volume of 65.5 ± 5.95 cc./Kg.

The following volumes (cc./Kg.) in cardiac patients were determined: 17 (who never had congestive failure) 61.3 ± 7.60, 8 (who previously had been in failure but were fully compensated during the determination) 66.6 ± 9.10, 12 (who had dyspnea, orthopnea and pulmonary congestion) 61.0 ± 6.60, 25 (who had pulmonary congestion plus either 2 or more of the following: venous distension, hepatomegaly, ascites, hydrothorax or peripheral oedema) 77.7 ± 9.5, 4 (who had primary pulmonary disease and right ventricular failure with venous distension, hepatomegaly and peripheral edema) 82.2 ± 7.64.

Hypervolemia was found in the majority of cardiacs with right ventricular failure but not in patients with left ventricular insufficiency or mitral insufficiency alone.

Comparison of the Hemodynamic Effects of Digitalis and of Mercurial Diuretics in the Treatment of Congestive Heart Failure. *Bertha Rader,* A. L. Berger and Warren W. Smith.** Department of Medicine, New York University College of Medicine, and the Third (New York University) Medical Division of Bellevue Hospital, New York City.

Digitalis, which is considered to have a primary myocardial action, and mercurial diuretics, which are considered not to affect the heart directly, can each restore patients with congestive heart failure to clinically similar degrees of cardiac compensation. It was the purpose of this study to determine whether the hemodynamic functions were similar or dissimilar in these 2 circumstances.

Hemodynamic functions were measured 3 times in each of 7 cardiac patients in sequence: (1) during decompensation before treatment, (2) during compensation achieved by mercurial diuretic therapy alone, (3) in the compensated state after full digitalization.

In 4 patients all of the hemodynamic functions improved after compensation was induced by mercurial diuretics, and were further improved, and brought to normal limits, following full digitalization. Furthermore, those who performed a standard exercise test showed a more normal response after digitalis. In 2 patients, who had the most advanced heart disease, neither mercurial diuretics nor digitalis produced any change in the circulatory functions after maximum clinical improvement. In the 7th patient, whose hemodynamics were only slightly abnormal in the decompensated state, improvement was induced by diuretics, and digitalization produced no further change.

This still incomplete study suggests that the compensation induced by mercurial diuretics may clinically simulate that induced by complete digitalization, but the hemodynamic status of the digitalized patient more closely approaches the normal. However, if the circulation is too impaired, or if the hemodynamics have not become markedly abnormal during decompensation, digitalis may not further improve the hemodynamic status achieved by diuretics.

Transcapillary Migration of Heavy Water and Thiocyanate Ion in the Pulmonary Circulation of Normal Subjects and Patients with Congestive Heart Failure. *Lawrence S. Lilienfeld,* Edward D. Freis, Edward Partenope and Harold J. Morowitz.** Cardiovascular Laboratory, Georgetown University Medical Center, Washington, D. C.

New technics for estimating the transcapillary migration of labelled permeable substances under physiologic conditions (J. Appl. Physiol. *5:* 526, 1953) have made it possible to compare the pattern of migration of water (D_2O) and an electrolyte (SCN) through the pulmonary capillaries in normals with the pattern obtained in patients with congestive heart failure. Six normal and 6 cardiac patients have been studied thus far. Consistent differences have been observed in the 2 groups.

Heavy water was handled differently from SCN in the pulmonary circulation of normal patients. In the normal there was an average outward migration of 40% of the injected D_2O (S.D. 7.1) during the early period of the 1st circulation and in the late portion of the 1st circulation a return of 33% (S.D. 21). By contrast, only small amounts of thiocyanate (1–2%) moved out of the capillaries at a fairly constant rate during the period of 1 circulation.

In the cardiac patients the outward migration of D_2O in the early phase of the 1st circulation was similar to the normals, averaging 35% (S.D. 12.6) of the injected material, but the return was less in the interval between the 1st and 2nd circulation, averaging only 7% (S.D. 4.3). The loss of SCN was significantly greater than in the normals, averaging 10 to 12% of the circulating material.

These studies demonstrate that the transcapillary migration of water and thiocyanate is abnormal in the lungs of patients with congestive heart failure in that the return of diffused water to the circulation is delayed and the transcapillary exchange of thiocyanate is increased.

Retrograde Transmission of Left Atrial Pressure Across the Pulmonary Capillary System. *Helmut Mueller,* Goffredo Gensini, Arthur E. Prevedel**

and Gilbert Blount, Jr. University of Colorado School of Medicine, Denver.

A double lumen catheter was introduced into the pulmonary artery of anesthetized dogs and wedged into a small branch. The chest was then opened and an 18 gauge needle introduced into the left atrium, and the pulmonary artery was completely constricted by a ligature proximal to the openings in the catheter. The left atrial pressure was altered by varying degrees of aortic constriction, and all pressures were recorded simultaneously.

Left atrial pressures below 30 to 40 mm. Hg were transmitted across the pulmonary capillary bed to the pulmonary arteries as mean pressures, while with pressures of a higher order, the cyclic changes of the left atrial contours were transmitted to these vessels. This demonstrated that pressure variations of sufficient magnitude occurring within the left atrium are transmitted in a retrograde manner across the pulmonary capillaries to the occluded pulmonary artery. Moreover, these studies indicate that the pressure contours obtained in the occluded pulmonary artery are a more sensitive reflection of the cyclic changes occurring in the left atrium than those recorded from the wedged catheter.

These results suggested the following conclusions: (1) That cyclic variations of left atrial pressure above a magnitude of 30 to 40 mm. Hg are transmitted across the capillary bed. (2) The retrograde transmission of left atrial pulse pressure variations are less damped when recorded in the occluded pulmonary artery than when recorded through the tip of the wedged catheter. The resistance to retrograde pressure transmission decreases with the increasing number of capillaries according to Poiseuille's formulations.

The Determination of Circulating Pulmonary Blood Volume in Normal Dogs by a Method Involving Arteriovenous Dye Equilibration. *Murray Rabinowitz, Elliot Rapaport, Hiroshi Kuida,* Florence W. Haynes,* and Lewis Dexter.* Medical Clinic, Peter Bent Brigham Hospital, and Department of Medicine, Harvard Medical School, Boston. (Aided by grants from the Life Insurance Medical Research Fund and the National Heart Institute, U. S. Public Health Service.)

Present methods for measuring pulmonary blood volume are based on arterial dye dilution curves representing a single circulation through the lungs. When intrathoracic volume is increased, complete mixing of dye within it may fail to occur.

A method patterned after Bradley's splanchnic blood volume technic was developed; it depends on thorough mixing of dye in the lungs, which is considered complete when equilibration within arterial, pulmonary artery, and presumably intrathoracic blood has occurred. Expressed mathematically

$$B = \frac{Ft\ (A - V)}{C}$$

where B represents pulmonary blood volume in cc.; F, cardiac output in cc./sec.; t, seconds from injection until equilibration; A, mean pulmonary artery concentration from injection to equilibrium; V, mean arterial concentration over the same period, and C, the dye concentration at equilibrium. Thus, the quantity of dye carried to the lungs minus that leaving over the period of equilibration when divided by the equilibration concentration measures the volume of the diluting space.

Eighteen determinations were performed on dogs using Evans-Blue Dye injected into the jugular vein or right atrium. Pulmonary and femoral artery samples were collected using a constant suction pump. Cardiac output was determined by direct Fick, and dye methods. Equilibration occurred between 57 and 127 seconds. Mean pulmonary blood volume was 246 cc./10 Kg. (σ = 32) and averaged 29% of the total blood volume. Values in individual dogs compared closely with those obtained by the "mean circulation time-output" method and were probably significantly higher than values obtained by the "slope-output" method.

The Response of Arterial Pressure to Changes in Intrathoracic Pressure: The Role of Peripheral Arterial Distensibility. *Henry D. McIntosh,* E. Harvey Estes, Jr.* and James V. Warren.* Department of Medicine, Duke University School of Medicine, Durham, North Carolina, and Veterans Administration Hospital, Durham. (Aided by grants from the American Heart Association and the National Heart Institute.)

Alterations of intrathoracic pressure are accompanied by changes in systemic arterial blood pressure. Although these changes have previously been studied, they have not been generally appreciated or fully elucidated.

A single cough was used to suddenly increase intrathoracic pressure. The peripheral arterial pressure and the differential pressure of the great vessels of the thorax (observed peripheral arterial pressure minus the intrathoracic pressure) were recorded using strain gages. These pulse contours were compared with those recorded before and after the cough.

Observations were made on 20 subjects without vascular disease. There was a sharp rise in peripheral arterial pressure with a cough. The differential intrathoracic pressure initially decreased but was followed by a rebound. These changes occurred with increases of intrathoracic pressure as small as 8 mm. Hg. Direct aortic measurements indicate that these findings were not artefacts related to standing waves. Five patients with marked peripheral vascular

disease had significantly smaller decreases in differential pressure.

Studies on a model indicate that the observed decrease in differential pressure is a result of a sudden "squeezing" of blood from the thorax into the peripheral vessels, thus decreasing the intrathoracic arterial volume and differential pressure. The magnitude of this effect is related to a large degree to the distensibility of the peripheral arterial system, the elasticity of the aorta being of little importance.

These observations emphasize the effect of *small* changes in intrathoracic pressure on the arterial pressure. Such studies may prove clinically useful in assessing the state of the peripheral vascular bed.

The Pharmacodynamics of Postural Hypotension. *Robert A. Schneider, Theodore Spengos* and Walter Joel.** Departments of Medicine and Pathology, University of Oklahoma School of Medicine and The Oklahoma Medical Research Foundation. Oklahoma City.

Two patients with multiple sclerosis who at autopsy showed degenerative changes in the hypothalamus had pronounced postural hypotension.

One of these individuals, who appeared to have a striking loss of central sympathetic tone, was carefully studied with reference to his response to pharmacologic agents including 1 drug, Thorazine (10 - γ - dimethylaminopropyl - 2 - chlorophenothiazine hydrochloride) whose hemodynamic effects have not been previously studied.

Two test procedures were used. The blood pressure was observed in the horizontal position, at 45°, and at 90°. Secondly, the Funkenstein test of central autonomic reactivity was used (blood pressure pattern in horizontal position following mecholyl).

On both tests the subject, without prior medication, exhibited marked decrease in central sympathetic reactivity. The blood pressure averaged 92 mm. systolic in the horizontal position, 68 mm. at 45°, and 45 to 0 mm. at 90°. The mecholyl test showed marked hypotension and a striking failure to achieve homeostasis.

Epinephrine and ephedrine largely blocked the hypotensive effect of gravity. This may have been due to its peripheral action. Centrally acting agents (Amytal, Thorazine and Rauwolfia Serpentina) fell into 2 categories. Amytal on both tests accentuated the depressor effect of gravity and mecholyl, while Thorazine and Rauwolfia Serpentina led to a striking reduction of these depressor effects.

These patients offered an unique opportunity to appraise pharmacodynamic agents which act on central autonomic function in that central sympathetic reactivity in these subjects was markedly reduced or absent. In individuals intact from the central autonomic standpoint, one is handicapped in knowing whether to ascribe the effect to a direct action of the agent or to an indirect effect of activating an antagonistic homeostatic response.

The Venous Pressure-Volume Curve of the Human Leg Measured In Vivo. *Julius Litter, James E. Wood* and Robert W. Wilkins.* Evans Memorial Hospital, Boston and Department of Medicine, Boston University School of Medicine. (Aided by a grant from the Life Insurance Medical Research Fund.)

The purpose of this study was to develop a method for obtaining venous pressure-volume curves of the leg which would be physiologically valid. Such curves should represent increases in venous volume, each of which was produced by the same known venous pressure in all the leg veins.

A constant reference point or baseline value of venous volume at an effective venous pressure slightly greater than zero in all the veins was obtained when the horizontal leg was placed in a water-filled plethysmograph and the water pressure on the leg was greater than the natural local venous pressure. The actual venous pressure in the leg was adjusted to equal an arbitrary pressure in a venous congesting cuff on the thigh by "titrating" the water pressure on the leg and recording volume changes. Then the congesting cuff pressure was increased 30 mm. Hg by increments of 5 mm. Hg and the corresponding increases in leg volume were recorded. Experimental evidence is presented indicating that these pressure-volume curves were produced by increasing the effective pressure in all the leg veins from slightly greater than zero to 30 mm. Hg by increments of 5 mm. Hg.

The curves are not affected by physiologic and pharmacologic changes in central venous pressure or peripheral blood flow and are determined by only 1 variable, the resistance of the veins to stretch. Accordingly, they are useful for the study of venous tone. The data in normal subjects is presented and the increase in venous tone produced by epinephrine and norepinephrine demonstrated.

Effect of Low Sodium Intake on Body Fluid Distribution in Hypertension. *Alvin P. Shapiro, H. C. Teng* and Arthur Grollman.** Departments of Internal Medicine and Experimental Medicine, Southwestern Medical School of the University of Texas. Dallas.

The evidence that body fluids and tissue sodium are increased in hypertensive vascular disease has revived the thesis that their depletion is responsible for the effects of sodium restriction in this disease.

In order to reexplore this problem, extracellular fluid (radioactive sulfate) and total body water (antipyrine) were measured in 6 patients with uncomplicated essential hypertension, during periods on regular diet and low sodium intake (less than

500 mg.). A consistent fall in ECF volume was observed in all the hypertensive subjects during sodium restriction (1.2 to 1.8 L., averaging 1.37 L.). The magnitude of this decrease showed no correlation with blood pressure change which in fact was not significantly affected by salt restriction in four of the patients. Weight decline was also consistent, ranging from 0.9 to 2.0 Kg., averaging 1.54 Kg. Change in TBW was quite irregular; it fell in 2 patients and rose in 3 others. (TBW not studied in one patient.) However, TBW:ECF rose in 4 and was unchanged in the 5th.

The data confirm the evidence that sodium restriction does not influence hypertensive vascular disease simply by depleting ECF volume and so lowering the blood pressure. The decrease in ECF was only equivalent to the expansion of this compartment previously observed in hypertensive humans and animals. Moreover, the TBW studies suggest that changes in osmotic equilibria occurred with salt restriction, resulting in a maintained, or actually increased, intracellular fluid volume. While the inherent difficulties of these methods when employed to measure the small changes herein involved do not permit definite conclusions, the results indicate that sodium restriction may affect the hypertensive process by altering a basic disorder in fluid and electrolyte distribution.

The Excretion of Salt in Hypertensive Individuals before and during Chronic Drug Therapy. *William Hollander* and Walter E. Judson.* Boston.

Fifteen patients with uncomplicated essential hypertension, 4 of whom had had lumbodorsal splanchnicectomy were infused with 300 cc. of 5% saline within 30 minutes both before and during chronic oral hypotensive drug therapy. Seven patients were treated with Apresoline, 5 patients with Apresoline and Rauwolfia, and 3 patients with hexamethonium.

Before drug therapy, independent of changes in renal plasma flow (PAH clearance), glomerular filtration rates (inulin clearance) and cardiac output (Fick), the rate of sodium excretion usually was 2 to 4 times greater than the rate observed in the 10 control (normotensive) individuals. After satisfactory hypotensive drug therapy, independent of changes in R.P.F., G.F.R. and cardiac output, the high rates of sodium excretion usually returned to, towards, or below normal.

One normotensive and 4 hypertensive individuals, when prepared on a salt-free diet and 250 mg. oral diamox 3 times weekly for 2 weeks without altering the blood pressure, had moderate and marked reductions in sodium excretion following acute salt loads.

Two normotensive individuals, when given high salt diets without altering the blood pressure, had increased rates of sodium excretion to the hypertensive range.

In 3 normotensive individuals the prior expansion of the extracellular fluid volume by chronic DOCA administration or with 2,000 cc. infusions of isotonic saline did not augment sodium excretion following acute salt loading.

The data suggest that the excretion of sodium following intravenous hypertonic saline may be a function of total body sodium. Studies are now in progress to determine the effects of hypotensive drugs on total body sodium.

Effects of Orally Administered "Veriloid" and "Rauwiloid" on the Blood Pressure of Hypertensive Individuals. *C. T. Bello and L. W. Turner.** Temple University Hospital and School of Medicine, Philadelphia. (Supported by AMA Grant 520–690.) ("Veriloid" and "Rauwiloid" were supplied by the Riker Laboratories, Los Angeles, California.)

Twelve patients from the hypertensive clinic of Temple University Hospital were selected for this study. These patients were considered a representative cross-section of types of essential hypertension. All patients in this study attended the hypertensive clinic for many months. In each instance, a control period with placebo therapy was instituted prior to the oral administration of veriloid and rauwiloid (alkaloids of rauwolfia serpentina). Veriloid was administered for 4 weeks in daily divided doses ranging 4 to 8 mg. Nightly doses of rauwiloid ranging from 1 to 2 mg. were administered in conjunction with the veriloid therapy for 4 weeks. Blood pressure readings were taken at weekly intervals under controlled conditions. Following the course of veriloid and rauwiloid these patients were again placed on placebo therapy. Blood pressure readings and symptoms, both subjective and objective, were recorded prior to, during and after veriloid and rauwiloid therapy. The combination therapy (veriloid with rauwiloid) failed to reduce blood pressure but produced a fall in the average pulse rate in most patients. The following symptoms: (1) headache (2) weakness (3) dizziness (4) nausea and vomiting were encountered in some of the individuals on the combined therapy. That the veriloid was absorbed when given orally was evidenced by the central or reflex effects induced, such as fall in pulse rate and nausea and vomiting. Rauwiloid therapy in the recommended dosage did not abolish the central or reflex-stimulating effects of veriloid on the vomiting center.

Comparative Effects of Intravenous and Chronic Oral l-Hydrazinophthalazine on the Cardiorenal Hemodynamics and the Excretion of Sodium in Hypertensive Patients With and Without Congestive Heart Failure. *Walter E. Judson and William Hollander.** Boston.

In 12 patients with arterial hypertension (compensated) acute intravenous l-hydrazinophthalazine

(Apresoline, Ciba), in dosage of 15 to 40 mg., produced significant increases in cardiac output (Fick, 52%) and renal plasma flow (PAH, 32%) without significant change in the glomerular filtration rate (inulin). Independent of the fall in the arterial pressure there was no significant change in the excretion of sodium and water. Furthermore, even when they were acutely salt-loaded they had no increase in sodium excretion after Apresoline. However, in 2 patients with vascular collapse antidiuresis and antisaluresis were observed. Two patients with congestive failure due to hypertensive cardiovascular disease showed a 10 to a 100-fold increase in sodium excretion associated with a marked increase in cardiac output (3-fold) and RPF (100%) with slightly significant increase in the GFR.

Simultaneous cardiovascular and renal function measurements of 10 of these patients were made before and during chronic oral treatment. During drug therapy the blood pressure in all of these patients had been moderated or maintained near normotensive levels for a period of at least 6 to 12 months. In 5 patients, 1 of whom was in congestive heart failure, treatment with the drug in dosages of 400 to 1,000 mg. daily produced a significant increase in RPF (over 25%). Likewise, 2 of this group had significant increases in GFR and cardiac output. In 1 patient the cardiac index was as high as 6.4 l./min./M^2. The patient with congestive failure on combination therapy was recompensated both, at rest and exercise as determined by clinical and physiologic assessment. In 2 other patients on chronic therapy an additional oral dose (50 mg.) caused an increase in cardiac output and RPF.

These data indicate that large acute and chronic doses of Apresoline in some patients produce alterations in cardiovascular and renal function similar to those observed with the acute intravenous administration of the drug. Oral and intravenous Apresoline, by lowering the blood pressure and promoting the excretion of sodium, may be of therapeutic value in the treatment of hypertensive cardiovascular disease with congestive failure. In some patients, however, with compensated hypertensive cardiovascular disease, Apresoline, by producing an abnormally high cardiac output, may not only prevent a satisfactory reduction in the blood pressure but increase the work of the heart.

Peripheral Resistance and Hypertension as Studied by Toe Plethysmography. *F. S. Caliva, R. H. Lyons and J. F. Harris.* Department of Medicine, Upstate Medical Center, State University of New York, Syracuse.

The purposes of this study are to determine, (1) if the vascular bed of the toe participates in the increased peripheral resistance in hypertension, and (2) if the nature of this resistance differs in the various stages of primary and secondary hypertension. Patients consisted of normotensives, both labile and fixed essential hypertensives and individuals with elevated blood pressures secondary to renal disease or endocrine pathology. In none was cardiac failure or peripheral vascular disease present. All were studied in a constant temperature room in the supine position. Blood flows to the toe were determined plethysmographically before and after a posterior tibial nerve block. Peripheral resistances were calculated by dividing the mean blood pressure by the blood flow.

It is found that in the resting state the peripheral resistance of the hypertensive group was significantly higher than that in the normotensive. After the abolition of local neurogenic tone, resistance of the abnormal patient fell into 2 groups. Those people without evidence of renal disease and with class 1 retinal changes exhibited peripheral changes in the normal range. Much higher values were found in most of the patients with primary or secondary renal disease, particularly those with azotemia or severe retinopathy. One patient with a theochromocytoma, 1 with Cushing's disease and another with concomitant hyperthyroidism also had high peripheral resistance following block.

It is concluded that the increased peripheral resistance in hypertension includes the vascular bed of the toe. This increased resistance in some individuals may be mainly on a neurogenic basis, since it may be reduced to normal following local sympathetic block. In other patients, another mechanism must also be operative. The digital plethysmograph provides a way to separate these types.

Pattern of Skin Temperature Response to Vasodilator Agents. *Lothar Wertheimer,* Walter Redisch and J. Murray Steele.** Research Service, Third (New York University) Medical Division, Goldwater Memorial Hospital, New York.

The pattern of surface temperature response in man to an environment of 20°C. and 55% humidity, under basal conditions, is predictable: e.g., while toe (glomus area) temperature decreases to values close to 20°C. and remains there, forehead (blush area) temperature remains constant at about 34–35°C. throughout.

Against this background 12 agents presumed to cause vasodilatation were tested. Each agent was tested anywhere from 3 to 13 times.

Nicotinic acid (100 mg. i.v.) and Roniacol (100 mg. i.v.) produced a regular increase of temperature of the blush area (2.4 and 1.8°C. average, respectively) without change in the glomus area.

In contrast, nearly all the others, tetraethylammonium chloride (300 mg. i.v.), diethylaminoethanol (4.3 mg. i.v.), Priscoline (50 mg. i.v.), Hydergine (0.3 mg. i.v.), Ilidar (3 mg. i.v.), hexamethonium (10 mg. i.v.), and Dibenzyline (120 mg. p.o. for 4 weeks) regularly produced an increase in temperature of the glomus area (averaging from 1.5 to 5.0°C.) without change in the blush area.

Nitroglycerine (600 μg. sublingually in the recumbent position) produced decrease of temperature in the glomus area (averaging 1.4°C.) in 4 experiments, while there was no change in 3. Change in the blush area was not observed.

Aminophylline (225 mg. i.v.) and 5% Saline (250 ml. i.v.) produced no change in either blush or glomus area.

Body temperature showed no significant variations during any of the experiments reported.

Thus it emerges that different vasodilator agents affect selectively different vasomotor areas in the human skin.

Serum Mucopolysaccharides in Diabetic and Nondiabetic Patients with Degenerative Vascular Disease. *Harold Rifkin, James Berkman* and George Ross.** Medical and Laboratory Divisions, Montefiore Hospital, New York City.

In the search for factors responsible for the development of atherosclerosis, interest has centered about the role of abnormalities of circulating lipids. However, it has been apparent that factors other than, or in addition to disordered lipid metabolism, may be decisive. In particular, morphologic and chemical evidence that a fundamental disturbance of the complex mucopolysaccharide ground substance of connective tissue precedes the subintimal deposition of lipids in the vessel wall is being expanded and reevaluated with increasing enthusiasm.

Human serum contains, bound to proteins, a relatively high concentration of complex polysaccharide. The source, composition and function of which are poorly understood. However, that the distribution and concentration of these substances are altered in a wide variety of diseases has been demonstrated repeatedly. It has been suggested that these changes reflect the release into circulation of substances derived from complex tissue carbohydrates as the result of tissue injury.

This report is based on a comparative study of certain polysaccharide components in the serum of diabetic patients and nondiabetic patients with degenerative vascular disease. We have reported previously (J. Clin. Invest. *37:* 415) that the concentrations of total nonglucosamine polysaccharides bound to serum protein and of the serum glucosamine are significantly increased in diabetic patients, but only when clinically detectable degenerative vascular disease exists.

In a few nondiabetic patients with well-established cerebral, coronary, renal or peripheral arteriosclerosis, the total nonglucosamine polysaccharides bound to serum protein are also elevated, and to a degree comparable to that in the diabetic group. However, in contradistinction to the pattern in diabetic patients, in the great majority of nondiabetic individuals with degenerative vascular disease, the values for total polysaccharides and for the serum glucosamine are normal or very slightly elevated.

While the quantitative interrelationship of nonglucosamine polysaccharides bound to serum protein and the serum glucosamine is not known, these observations suggest that there are differences of the serum glycoprotein patterns in the categories of patients studied. The possible significance of this observation, with particular emphasis on the pathogenesis of diabetic, as well as nondiabetic degenerative vascular disease, is discussed.

Observations of Cardiovascular and Renal Hemodynamic Responses to Reserpine (Serpasil) and Clinical Results in Treatment of Hypertension. *John H. Moyer, Warren Hughes* and Russell Huggins.** Baylor University College of Medicine, Houston, Texas.

Observations have been made on the cardiovascular and renal hemodynamic response to reserpine administration to laboratory animals and patients with hypertension. A reduction in blood pressure occurred after reserpine (Serpasil) was administered intravenously to laboratory dogs and human patients, but there was no consistent effect on cardiac output or on renal hemodynamics except that peripheral vascular resistance was reduced and GFR was slightly reduced in the patients but not in the dogs. In patients with hypertension, there were no alterations in GFR or in RBF after oral administration for 3 months or more, despite a significant blood pressure reduction in 6 out of 8 patients treated. Plasma concentrations of electrolytes and excretion of these agents by the kidney were not altered. Sixty-two patients with variable degrees of hypertensive vascular disease who have been treated with reserpine on an outpatient basis were observed. The results indicated a significant blood pressure reduction in about half of the patients treated for 2 to 8 months. One third of the patients became normotensive. No incapacitating side effects were noted, although bradycardia and sedation were frequently observed.

CENTRAL NERVOUS SYSTEM

An Electromyographic Study of a Spinal Cord Reflex in the Normal Human Arm. *R. J. Johns,* D. Grob* and A. M. Harvey** (Introduced by *J. L. Lilienthal, Jr.*). Johns Hopkins Hospital, Baltimore Maryland.

Two action potentials can be recorded from the hypothenar muscles following a single, submaximal, electrical stimulus applied to the ulnar nerve. The first of these potentials results from stimulation of efferent (motor) fibers of the ulnar nerve. There is evidence that the second is produced by stimulation of afferent fibers which in turn activate motoneurons via a spinal cord reflex arc. With sufficiently weak stimulation of the nerve this second action potential can be elicited without discernible direct motor response. This indicates that the threshold for stimulation of the afferent limb of the reflex arc is lower than that of the motor fibers. While the direct response increases with increasing stimulus strength, the size of the reflex response decreases. It is believed that as stimulus strength is increased more motoneurons are rendered refractory as a result of antidromic activation, and that they are therefore no longer available for reflex stimulation. Striking potentiation of the reflex potential may result from situations which produce increased activity of the hypothenar muscles, whether voluntary or incidental to a general increase in muscular activity. When a second stimulus is applied to the nerve 32 to 100 milliseconds after the first, the second stimulus evokes a single, direct motor response with diminution or absence of reflex response. At other intervals both stimuli produce direct and reflex responses of comparable amplitude. This reflex affords a method of studying effects of drugs and disease on human spinal cord activity.

Cerebral Circulation and Metabolism in Malignant Hypertension, with Observations on the Effects of Intravenous Administration of Bacterial Pyrogen. *John L. Patterson, Jr., Albert Heyman, Louis L. Battey,* and T. Whatley Duke.** Department of Medicine, Medical College of Virginia, Richmond, and Department of Medicine, Emory University School of Medicine, Atlanta.

The derangements in the cerebral circulation and metabolism associated with malignant hypertension were studied by the nitrous oxide method in 13 patients. Seven of these were restudied following administration of 0.07 to 0.1 cc. intravenous typhoid vaccine, in 2 cases blocked with aminopyrine. For comparison, the same observations were made in 4 patients with essential hypertension and comparable pressure elevation, in 3 of whom the pyrogen was blocked.

In the 13 patients with malignant hypertension the mean values for both cerebral blood flow (CBF) and oxygen consumption (CMR_{O_2}) were significantly reduced (20%) and vascular resistance (CVR) markedly and significantly increased (156%). Mean arterial blood pressure averaged 165 mm. Hg, as compared with 91 mm. Hg in 25 control subjects During the pyrogen reaction, the CBF and CMR_{O_2} rose to normal values, and the CVR fell 34% but remained above normal. In contrast, the patients with essential hypertension during the pyrogen reaction showed decreases of 22% in both CBF and CMR_{O_2}, together with a small (11%) fall in CVR. In normal individuals the pyrogen reaction produces little change in these functions.

The abnormalities in the CBF and CVR in malignant hypertension indicate a marked reduction in caliber of the cerebral vessels, a significant portion of which was reversible by pyrogen. It appears probable that the increase in oxygen consumption with pyrogen was largely due to the increase in blood flow, and that both changes may be related to the beneficial effects of pyrogen therapy. Paradoxically, the cerebral vasodilator response to the pyrogen reaction appears less active in essential than in malignant hypertension.

Cerebral Circulation and Metabolism in Hyperthyroidism and Myxedema. *Willis Sensenback,* Leonard Madison, and Seymour Eisenberg.** Department of Medicine, Southwestern Medical School of the University of Texas and the Department of Medicine, Veterans Administration Hospital, Dallas.

The nitrous oxide method for the determination of cerebral blood flow has been employed in this study of the cerebral circulation in hyperthyroidism and myxedema. Cerebral hemodynamic and metabolic functions were studied in 22 hyperthyroid and 11 myxedematous male subjects. In 16 of the hyperthyroid and 8 of the myxedematous subjects, the studies were repeated after a euthyroid state had been induced by appropriate treatment, and these values served as controls for comparison with the pretreatment findings.

Hyperthyroidism is accompanied by a 42% ($p = <.001$) increase in mean CBF, a 35% ($p = <.001$) decrease in mean CVR, and a 7% ($p = <.01$) decline in mean arterial blood pressure. Myxedema by contrast is accompanied by a 22% reduction in mean CBF ($p = <.001$), a 48% increase in CVR ($p = <.01$), and a 16% increase in mean arterial blood pressure ($p = <.05$).

Arterial-cerebral venous oxygen difference changed in a reciprocal fashion to CBF. In hyperthyroidism mean arterial-cerebral venous oxygen difference decreased 18% ($p <.001$), whereas in myxedema arterial-cerebral venous oxygen difference increased 17% ($p = <.01$). Neither hyper- nor

hypothyroidism is associated with a change in cerebral O_2 or glucose consumption.

The results show that the brain participates in the general circulatory alterations that accompany variations in the functional activity of the thyroid gland. The rate of cerebral oxygen and glucose utilization, however, is apparently uninfluenced by thyroid function.

The Blood Flow and O_2 Consumption of the Human Brain in Hepatic Coma. *Richard L. Wechsler, William Crum,* and James L. A. Roth.* Departments of Gastroenterology, Anaesthesiology, Physiology and Pharmacology, Graduate School of Medicine, University of Pennsylvania, and Division of Cardiology, Philadelphia General Hospital, Philadelphia.

Hepatic coma is a systemic disease with profound effects on the central nervous system and an extremely high mortality rate.

Cerebral blood flow (CBF) was measured by the N_2O technic in 7 male patients in hepatic coma. Results were compared to those of a similar age group (J. Clin. Invest., *32:* 459, 1953). Alkalosis (arterial pH 7.48, $p < 0.001$) was found presumably the result of the observed hyperventilation, vomiting and/or alkali therapy. No change in cerebrovascular resistance (CVR) (2.4 mm. Hg/cc./100 Gm./min., $p < 0.3$) was noted in spite of the significant decrease in arterial pCO_2 (25 mm. Hg $p < 0.001$). The anemia (11.5 Gm.) and alkalosis should decrease CVR. Despite this constant CVR, the CBF fell significantly to 33 cc./100 Gm./min. ($p < 0.01$), as a result of a significant decrease of mean arterial blood pressure (78 mm. Hg $p < 0.01$). With the decreased CBF and lack of change in the arteriovenous O_2 difference (5.23 vols.%, $p < 0.4$), a low cerebral metabolism (CMR_{O_2} 1.7 cc./100 Gm./min. $p < 0.001$) resulted. This depression of CMR_{O_2} is unrelated to serum bilirubin levels ($r = +0.26$, $p \gg 0.1$).

Arterial O_2 saturation (93%, $p < 0.1$) was not significantly reduced. In spite of the respiratory and/or metabolic alkalosis, increased organic acid levels were postulated in order to explain the results of electrolyte studies. There was a greater depression of cerebral metabolism than of CBF and Hb, indicating a greater supply of O_2 to the brain than it was able to utilize. These results implicate an intracellular metabolic abnormality in the brain as the cause for the reduction in cerebral metabolism and coma in severe liver disease.

Alterations of the Acid Base Balance in Craniocerebral Trauma. *Albert W. Cook and E. Jefferson Browder.** The Neurosurgical Service of the Kings County Hospital, Brooklyn and the Department of Neurology and Neurosurgery of The State University of New York, College of Medicine, New York City.

In view of the persistent unsatisfactory understanding and the resulting inadequate therapeutic endeavors in instances of severe craniocerebral trauma, information was sought concerning the metabolic alterations under such circumstances.

Changes in the acid base balance were studied in 30 patients, all of whom had sustained varying degrees of craniocerebral trauma. The great majority of instances represented situations of severe general cerebral insult.

Estimations of the acid base balance were made by daily determination of the blood pH, carbon dioxide content, plasma bicarbonate, blood urea, hematocrit and electrolytes.

In the severe head injury group (18) 4 patients survived and in each of these there was no alteration of the acid base mechanism or the respiratory cycle. The remaining patients who had suffered severe craniocerebral injury all died, and all manifested varying degrees of change in the respiratory mechanism as well as severe alteration of the acid base balance. The primary prevailing disturbance was that of acidosis, respiratory, metabolic or mixed. In those patients with elements of metabolic acidosis, nitrogenous retention is markedly evident.

In the group of mild and moderate head injuries with or without associated intracranial clots there were no deaths and in no instance was there an irreversible respiratory or metabolic change.

It is apparent that in patients with severe craniocerebral injury associated with alteration of the respiratory mechanism and ventilatory capacity, severe metabolic disturbances (namely, uncompensated acidoses of all types) are a constant factor. The single factor that distinguishes those instances which result in fatal issues from those in which survival is evident is the presence or absence of respiratory alteration and attendant uncompensated changes in the acid base balance.

Pulmonary Mechanics in Patients with Poliomyelitis Involving Muscles of Respiration. *Bertrand C. Kriete,* Benjamin G. Ferris, Jr.* and Leon E. Kruger** (introduced by *James L. Whittenberger*). Harvard School of Public Health, Boston.

A low pulmonary compliance (reduced lung distensibility) has been reported previously in patients with respiratory muscle weakness secondary to poliomyelitis. These studies have been extended to include an additional 51 patients with poliomyelitis; 24 of this number were observed in the acute febrile stage. Nonparalytic and bulbar as well as spinal paralytic patients were included. The age range was 8 to 34 years.

All patients demonstrated a reduction in lung compliance below the predicted value. The values in the adults ranged from 0.07 to 0.20 L. per cm. H_2O (normal range 0.13 to 0.32). Lower values were generally found in children. A similar decrease in the compliance of the thorax also was seen. These changes in the lungs were already present within a few hours after hospital admission (i.e., within 2 days of the onset of fever) even in the absence of demonstrable weakness of respiratory muscles.

The reduction in compliance was approximately proportional to the reduction in vital capacity observed in these patients. During convalescence, however, although the vital capacity increased, the lung compliance remained unchanged in follow-up studies performed 2 months later.

Similar changes in vital capacity and in lung compliance have been noted in 3 patients with febrile illness other than poliomyelitis.

Values for total lung capacity in 18 patients show a direct relationship with the values for pulmonary compliance.

The processes underlying these changes are not known. Multiple focal atelectases in the acutely ill patient may be in part responsible.

Values for pulmonary resistance in 18 convalescent patients were within normal limits (< 4 cm. H_2O per L. per second).

COLLAGEN DISEASES—ALLERGY

The Relative Importance of Antigen and Antibody in the Pathogenesis of Rheumatic Fever. *Alton J. Morris,* Frank J. Catanzaro, Robert Chamovitz,* Chandler A. Stetson and Charles H. Rammelkamp, Jr.* Streptococcal Disease Laboratory, Francis E. Warren Air Base, Wyoming, and the Department of Preventive Medicine, Western Reserve University, School of Medicine, Cleveland. (This investigation was conducted under the sponsorship of the Commission on Acute Respiratory Diseases and the Streptococcal Disease Commission, Armed Forces Epidemiological Board, and supported by the Office of the Surgeon General, Department of the Army, Washington, D. C.)

The attack rate of rheumatic fever following acute streptococcal pharyngitis can be correlated with the magnitude of the antistreptolysin response. Similarly, experience indicates that the development of rheumatic fever probably depends upon the persistence of the infecting organism. Since the antibody response in streptococcal infections is a function of the persistence of the organism, it is difficult to distinguish between these factors. If such a distinction could be made, certain aspects of the pathogenesis of rheumatic fever might be clarified.

The present study was undertaken to determine whether rheumatic fever could be prevented by the eradication of the streptococcus subsequent to marked antigenic stimulation. In 450 patients with exudative pharyngitis, penicillin therapy was begun 9 days after the onset of clinical pharyngitis. With this interval before the onset of therapy, there is sufficient opportunity for considerable antibody production. A group of 450 patients served as controls. The results of the study indicate that delayed therapy with penicillin eradicated the infecting organism and significantly reduced the attack rate of rheumatic fever, although the antibody response was only slightly inhibited. These data have certain implications concerning the pathogenesis of rheumatic fever which should afford a more rational approach to the care of patients with streptococcal infections and rheumatic fever.

The Experimental Production of C-Reactive Protein in Human Beings and Cx-Reactive Protein in Rabbits before and during the Administration of Cortisone and ACTH. *G. H. Stollerman, S. J. Glick* and H. C. Anderson.** Irvington House and the Department of Medicine, N.Y.U. College of Medicine, New York City.

The detection of C-reactive protein (CRP) in the blood has been shown to be a highly sensitive and reliable test for the presence of inflammatory disease. During effective treatment with cortisone, ACTH or salicylates, CRP usually disappears from the blood of patients with acute rheumatic fever. Its disappearance may accurately reflect suppression of the inflammatory process or may be a direct metabolic effect of these therapeutic agents. An attempt was made to determine whether the latter possibility could be excluded.

Typhoid vaccine was administered as a single intravenous dose to 9 patients who had recovered completely from a recent attack of acute rheumatic fever. Blood samples obtained at frequent intervals during a period of 1 week were tested for the presence of CRP. The procedure was repeated during the administration of large doses of cortisone, ACTH or salicylates to the same patients. The promptness, intensity and duration of the CRP response was not altered by the administration of cortisone, ACTH or salicylates.

Similar experiments were performed in rabbits. Pneumococcal skin infections were induced as a stimulus to the production of Cx-reactive protein (the rabbit analogue of human CRP). Treatment with cortisone or with ACTH did not significantly alter the Cx-reactive protein response.

This study lends support to the concept that the disappearance of CRP from the blood during antirheumatic treatment is a result of suppression of the inflammatory disease rather than a direct effect upon CRP metabolism.

Effect of Orally Administered Compound F upon Acute Rheumatic Fever. *H. B. Houser, and H. A. Feldman.* Department of Medicine, State University of New York, Upstate Medical Center, Syracuse. (Aided by a grant from the Masonic Foundation for Medical Research and Human Welfare.)

Eighteen children with acute rheumatic fever (14 with carditis) were treated with orally adminis-

tered Compound F because available evidence suggests that this substance is the principal corticoid produced by the adrenal gland following stimulation by corticotrophin and further, that it is physiologically more potent than cortisone.

Experience derived from the treatment of the first 2 patients resulted in the adoption of the following schedule for the remainder. During the initial 24-hour period, 300 mg. of Compound F were administered in 4 doses followed by 200 mg. per day until certain clinical criteria were no longer present. At 4-day intervals, the daily dose was reduced by 40 mg. If clinical activity reappeared, the preceding dose was reinstituted and continued until reduction was again possible.

With this schedule there was prompt relief of arthritis, fever, tachycardia, precordial pain, and malaise. Heart failure was not present in any patient after 5 days of treatment. Pericardial friction rubs persisted for several days. There appeared to be no influence on the appearance and persistence of significant murmurs. The erythrocyte sedimentation rate was lowered during treatment but usually increased after cessation of treatment. Side effects of therapy appeared to some degree in all patients as did a reduction in the circulating eosinophiles. Following cessation of treatment, 14 patients had clinical or laboratory rebounds which subsided spontaneously in all but 2 patients who were retreated. Twelve patients had systolic and/or diastolic murmurs remaining up to several months following the onset of the acute rheumatic fever.

In summary, the response to treatment with Compound F was of the order expected with adequate doses of aspirin, cortisone, or ACTH.

Blood Glutathione Levels in Normals, Osteoarthritis, Rheumatoid Arthritis, Lupus Erythematosus Disseminatus and Dermatomyositis as Influenced by Steroid, Gold and Potassium Arsenite Therapy. *Robert E. Barkin,* Mary F. Massod* and Theodore B. Bayles.* Department of Medicine, Harvard Medical School, and the Medical Service of the Robert Breck Brigham Hospital, Boston. (Aided by Grant A-161, United States Public Health Service.)

Glutathione, important in carbohydrate metabolism, has been reported as being altered in rheumatoid arthritis and other connective tissue disorders, especially during ACTH and cortisone therapy. We have studied blood glutathione levels in these diseases as influenced by ACTH, cortisone, gold and potassium arsenite therapy.

Glutathione has been determined in hospitalized patients and normal controls free of fever, severe liver disease, ketosis and mental disease, which alter glutathione levels. Anemia has been corrected by the formula,

$$\frac{\text{mg. \% blood glutathione}}{\text{Hematocrit in mm.}} \times 100 = \text{GSH index}$$

Blood glutathione has been determined by: (1) Woodward and Fry method, and (2) The Bichel modification of (1), as standardized by Altschule and Henneman (immediate precipitation of blood proteins, procedures at 0°C.).

Results are reported as mg. glutathione per 100 cc. of packed red cells; 635 determinations have been made.

Blood glutathione levels in normals have a range of 47 to 91; the mean is 74. The levels in osteoarthritis are the same.

Patients with rheumatoid arthritis, regardless of the activity of the disease, have normal blood glutathione levels. There was no significant alteration during or after treatment with cortisone (100 to 500 mg. per day), gold salts or potassium arsenite. During 8-hour intravenous ACTH therapy, the blood glutathione was elevated.

Glutathione was depressed in severe lupus erythematosus disseminatus.

Conclusions: Abnormalities in sulfhydryl mechanisms, as measured by blood glutathione levels, have not been proved to play an important role in connective tissue diseases.

Changes in the Synovial Fluid Proteins in Rheumatoid Arthritis. *David Platt,* K. Lemone Yielding,* Howard L. Holley and Ward Pigman.** Departments of Biochemistry and Medicine, Medical-Dental Schools, University of Alabama, Birmingham. (Aided by a research grant A216 (C) from the National Institute of Arthritis and Metabolic Diseases, of the National Institutes of Health, Public Health Service.)

Qualitatively the proteins in synovial fluid resemble those of blood serum. In rheumatoid arthritis the increase in the concentration of the globulin fraction parallels the severity of inflammation. Similarly, a decrease in the mobility of the globulin fraction can be shown. Upon improvement of symptoms, the electrophoretic mobilities of the alpha-2 and beta globulins increase. The values obtained for normal synovial fluid indicate that the increase in speed of the components upon clinical improvement is further extended until the mobilities reach the normal value.

The A/G ratio (measured from electrophoretic patterns) in normal fluid was approximately 2/1, which agrees with the values obtained for normal serum. In rheumatoid arthritis, the A/G ratio ranged from 1/1 to 1/3, but no significant change could be noted upon clinical improvement.

The electrophoretic analyses of synovial fluid were carried out using the Perkin-Elmer Model 38 Tiselius electrophoresis apparatus. The buffers used in this investigation were veronal buffers at pH 8.1 and 8.6, ionic strength 0.1. The relative mobilities were determined by comparing the mobilities of the various components with that of the albumin fraction.

Analysis of the β-Glucuronidase Concentration of Synovial Fluid of Patients with Rheumatoid Arthritis and Degenerative Joint Disease. *Alexandra Feldmahn* and Ralph F. Jacox.* Department of Medicine, University of Rochester School of Medicine, Rochester, New York. (Aided by a grant from the Masonic Foundation for Research in Rheumatic Diseases.)

Fifty-six patients with various types of disturbance of joint function have been studied by estimating the concentration of β-glucuronidase of the synovial fluid. After aspiration of the knee or elbow joint, the β-glucuronidase activity was assayed by determining the free phenolphthalein split from the substrate, phenolphthalein glucuronide. The enzyme concentration was then expressed as γ of phenolphthalein/ml. of joint fluid/hr.

This study reveals that synovial fluid obtained from patients with degenerative joint disease contained low concentrations of enzyme (0.015–0.080 γ). Fluids of patients with mild rheumatoid arthritis contained 0.190–0.800 γ, while the concentration in severe rheumatoid arthritis ranged between 0.800–1.6 γ. Very high concentrations were found in pyogenic joint disease (2.0–19.7 γ). Serial assays of synovial fluid for β-glucuronidase may indicate the course of the disease and have prognostic significance. Determination of β-glucuronidase is helpful in differentiating degenerative joint disease from rheumatoid and pyogenic arthritis.

The relationship of synovial fluid glucuronidase to polymorphonuclear leukocytes is discussed.

Skin Sensitizing Antibody in Rabbit Antisera. *John H. Vaughan and Elvin A. Kabat.** Department of Medicine, Medical College of Virginia, Richmond and Departments of Microbiology and Neurology, College of Physicians and Surgeons, Columbia-Presbyterian Medical Center, New York City.

The abilities of rabbit antisera to crystalline egg albumin, crystalline conalbumin, and whole egg white to induce in human skin a wheal and erythema type of sensitivity have been compared with their contents of antibody to the major egg white antigens, egg albumin, conalbumin, ovomucoid, and lysozyme. Antibody analyses were done by quantitative precipitin technics and the sera examined by Oudin's agar diffusion method. Antibodies to numerous constituents of egg white were noted in all antisera, the extent and multiplicity of this antibody response being greater with more prolonged immunization. The capacity to sensitize skin was also more pronounced with more prolonged immunization. There was no correlation between sensitizing capacity and any of the measured antibody levels. Specific antibody absorptions with the available purified egg white antigens failed to reduce sensitizing capacity significantly. Skin sensitizing antibody appeared to be of 2 types, each characterized by a distinguishing pattern when the various purified egg white antigens were used to elicit the reactions; examples of both types of antibody were seen among the antisera to each of the 3 materials used for immunization.

The data indicate that there are 2 distinct egg white antigens capable of inducing formation of rabbit antibody that will sensitize human skin. Antibody to egg albumin, conalbumin, ovomucoid, and lysozyme are incapable of such sensitization, but antisera to these materials may contain skin sensitizing antibody because of traces of these skin sensitizing antigens present as impurities in them. Skin sensitizing antibody was unrelated to non-precipitating anti-egg albumin or anti-conalbumin.

ENDOCRINES AND METABOLISM

Carbohydrate Metabolism • Protein Metabolism • Water and Electrolyte Metabolism • Adrenal Cortex • Testis • Thyroid

Food Intake and Carbohydrate Metabolism. *Albert J. Stunkard* (introduced by *Lawrence E. Hinkle, Jr.*). Department of Medicine, New York Hospital-Cornell Medical Center, New York City.

A recent theory has proposed that the regulation of food intake is a function of the carbohydrate metabolism of the body. More particularly, food intake is stimulated by impoverishment of the available carbohydrate stores and inhibited by their replenishment. This theory was tested by a series of observations on a healthy young male subject with no history of weight or endocrine abnormalities. Peripheral arteriovenous glucose differences, considered as indicators of the status of the carbohydrate stores, were correlated at intervals of 45 minutes to 2 hours throughout the day with the subjective experience of hunger and satiety. When the arteriovenous glucose differences were greater than 10 mg. % satiety was always present; in no instance was hunger experienced. With arteriovenous glucose differences of less than 10 mg. %, hunger was observed although it was not invariably present in such circumstances. It appeared as if other factors, such as emotions and the duration of the small arteriovenous difference, play contributory roles in the development of the experience of hunger.

The influence of these emotional factors was observed in 2 patients with inlying gastric balloons. In the presence of a small arteriovenous glucose difference the experience of hunger as well as salivation and gastric hunger contractions could be induced by friendly discussion of appetizing food.

Twenty minutes later, when the infusion of glucose had resulted in an arteriovenous difference greater than 10 mg. %, such discussion had no effect on hunger, salivation or gastric contractions.

The Effects of Glucose and Fructose on Blood and Urine Ion Concentration. *Arvin S. Glicksman, Kathleen E. Roberts,* Rulon W. Rawson,* and Henry T. Randall.** Department of Medicine, Department of Surgical Physiology, Memorial Center for Cancer and Allied Diseases and the Sloan Kettering Institute, New York City.

The renewal of interest in fructose as an infusible hexose has led to a need for more exact information concerning the electrolytic responses to this infusion.

In this study, nondiabetic and diabetic patients were used, each patient serving as his own control for glucose and fructose effect, with and without insulin. After base line blood and urine studies were drawn, the diabetic patients received infusions of 10% glucose and water, 10% fructose and water, 10% glucose and water plus 50 units of regular insulin, and 10% fructose and water plus 50 units of regular insulin on successive days; the nondiabetic received infusions of 10% glucose and water and 10% fructose and water. Blood samples, urine specimens and EKG's were taken at 1 hour, 2 hours, 4 hours, and 6 hours after the onset of infusions. The blood samples were analyzed for glucose, fructose, CO_2, sodium, potassium, chloride and phosphate. The urine specimens were examined for volume, pH, glucose, fructose, sodium, potassium, phosphate and chloride.

No consistent or significant differences were noted in the handling of glucose or fructose in the diabetic and the nondiabetic. The changes in electrolytes and increased urinary volume and ion excretion are compatible with the introduction of a hyperosmotic diuretic in the form of a 10% hexose solution.

Observations on the Distribution of Glucagon (Hyperglycemic-Glycogenolytic Factor), Labeled with Radioactive Iodine. *Paul P. VanArsdel, Jr.,* Robert H. Williams,* and Neil Elgee** (introduced by *Clement Finch*). Department of Medicine, University of Washington School of Medicine, Seattle. (Aided by a grant from the National Institute of Arthritis and Metabolic Diseases.)

Glucagon has recently been labeled with I^{131} by a method used for labeling insulin first reported by Ferrebee et al. Investigations have been carried out to determine the effect of iodination on the hyperglycemic potency, and to ascertain the stability of the bond between I^{131} and the glucagon molecule: these will be discussed. The tagged glucagon was given to albino rats, and its distribution and concentration observed in total carcasses and in various individual tissues. Concentration of radioactivity by kidney was rapid, reaching 10 times plasma concentration within 5 minutes. Renal cortex showed 7 times the concentration of renal medulla. In order of descending concentrations, radioactivity was found in thyroid, blood, liver, duodenum, salivary gland, pancreas, lung, spleen, lymph node, pituitary, stomach, adrenal, heart, skin, jejunum, ileum, thymus, large intestine, muscle and fat. Insignificant amounts were present in testis and brain. The amount of radioactivity precipitable with trichloracetic acid ("glucagon radioactivity") was determined in several tissues. This amounted to 85–90% of the total radioactivity in carcass, liver and kidney 5 minutes after administration of tagged glucagon, but dropped rapidly to less than 20% 1 hour following administration. This fall was even more precipitous in muscle, while in blood 45% of the radioactivity was still protein-bound 1 hour following injection. Interpretation of the above data, and also data on the changes in distribution and degradation brought on by administration of excess insulin, epinephrine, and growth hormone, are correlated with the present accepted theories of glucagon action, distribution, and breakdown.

Effect of Glucagon on Peripheral Glucose Utilization in Man. *Theodore B. Van Itallie,* Mary C. Morgan* and Louis B. Dotti** (introduced by *James G. Hilton*). Departments of Medicine and Biochemistry, St. Luke's Hospital, New York City.

Experiments have been performed to determine the effect of glucagon (HGF) on peripheral glucose utilization in man. A highly purified glucagon preparation was administered intravenously to normal human subjects, and capillary (arterial) and antecubital venous samples were obtained for glucose analysis virtually simultaneously before and at frequent intervals during and after glucagon infusion. In control studies, usually involving the same subjects, (a) epinephrine was injected subcutaneously and then glucose was given by mouth, and (b) glucose was infused to simulate the hyperglycemia induced by glucagon. After glucagon administration, capillary glucose increments ranged from 40 to 80 mg. % above the control level. Comparison of A-V differences following glucagon administration with those following infusion of glucose showed that peripheral utilization of glucose was *not* inhibited by glucagon. By contrast, epinephrine administration was followed by striking inhibition of peripheral glucose utilization.

Formation of Serum Phospholipid in Clinical Diabetes Mellitus. *Charles R. Shuman, Jean Meszaros* and Robert Robbins.* Temple University Hospital and School of Medicine, Philadelphia.

In uncontrolled diabetes mellitus there is an increased rate of mobilization, transport and utilization of endogenous fat. In this study it was pro-

posed to examine the possible participation of phospholipid in the enhanced fat oxidation associated with diabetic ketosis. Nine patients with uncontrolled diabetes were given a measured dose of P^{32} and the rate of newly-formed phospholipid determined in serum samples obtained at specified intervals. Insulin was withheld during the 3 days required for this study. After an interval of 2 to 6 months, the tests were repeated on 8 patients under the same conditions except that careful diabetic control was maintained throughout the second study. The appearance rate constant for new phospholipid was found by subtracting the percentage of the P^{32} dose in the phospholipid fraction in each specimen examined from the maximum percentage reached for that patient.

The results of the radioactive phosphorus study indicate that there is no change in the rate of appearance (0.03 ± 0.01 per hour) of phospholipid in the serum of uncontrolled diabetics compared to that observed after an adequate period of stabilization. In addition, the appearance rate constants obtained in a group of nondiabetic control subjects were comparable to those observed in the diabetics. There was no influence of the action of insulin and restored glycolysis upon serum phospholipid formation. The failure to observe an elevated rate of serum phospholipid formation in uncontrolled diabetics casts doubt upon the role of this lipid fraction in the transport and oxidation of fats.

The Fate of Intravenously Administered Human Serum Albumin in a Patient with Anorexia Nervosa. *Philip H. Henneman, Anne P. Forbes and Fuller Albright.** Department of Medicine of the Massachusetts General Hospital and the Harvard Medical School, Boston.

Following the intravenous administration of albumin to patients on balance studies three "fates" have been identified. A portion of the albumin is "converted" to protoplasm, as indicated by a decrease in urinary phosphorus; a portion is "burned," as indicated by an increase in nonprotein nitrogen excretion; and a portion remains "unchanged," as indicated by the difference between total albumin administered and the sum of that "burned" plus that "converted."

A 31 year old woman with anorexia nervosa was studied for 12 days control, 12 days on 50 Gm. albumin i.v. daily, 24 days of control, 12 days on albumin plus 800 additional calories as glucose daily, and 12 days of final control.

The results of this balance study indicate a "fate" pattern very different from the normal. Whereas it might be anticipated that the starving person would either "burn" a larger fraction of administered albumin than the normal to supply calories, or would "convert" a larger portion to much-needed protoplasm, in fact this study demonstrated less "conversion" than normal and virtual absence of "burning." These "fates" of albumin were little altered by the concomitant administration of extra calories as glucose.

Thus, it would appear that the starving person conserves serum albumin by decreasing the rate of "burning" and "converting" and thus is relatively incapable of rapidly "burning" or "converting" a sudden influx of albumin. The situation is analogous to the familiar carbohydrate intolerance which follows a low carbohydrate intake.

Metabolism of Carnitine in Man. *Barbara Ansell,** *P. K. Bhattacharyya,** *Dolores Rix** *and Robert M. Kark.* Department of Medicine, University of Illinois College of Medicine and the Department of Entomology, College of Liberal Arts, University of Illinois. (Supported in part by a grant from the Nutrition Foundation, Eli Lilly and Company and the Muscular Dystrophy Association.)

While investigating the folic acid requirements of insects, Fraenkel found that the meal worm (*Tenebrio mollitor*) required another factor, not previously recognized, for normal growth and development. He named this factor, which was present in the charcoal filtrate of yeast, vitamin B_T. Later, he developed a bioassay method for vitamin B_T. He used the rate of growth and survival of the larvae of *Tenebrio mollitor*, living on a synthetic diet, as the method of analysis. By bioassay he found that there was a wide distribution of the vitamin in nature and, in particular, found large amounts in mammalian muscle (1 mg. per Gm. of dry weight). Recently, Vitamin B_T was found to be identical chemically with carnitine, a quarternary ammonium compound which originally had been isolated from muscle and meat extract in the early part of the twentieth century. Although muscle is the most potent source of carnitine, it is also present in blood and urine. Its wide distribution suggests that it serves some vital function. Since the bioassay is tedious and difficult to run, we have recently developed a biochemical method of assay. The carnitine from body fluids and muscle is split to trimethylamine, after being absorbed on Dowex columns. The trimethylamine gives color reactions with a variety of agents. The concentration of these colors is measured on a spectrophotometer. The method will be described, as well as our observations on carnitine in blood, urine and muscle from healthy individuals living on normal and high protein diets. Preliminary observations on patients with muscular diseases indicate that carnitine levels are considerably reduced in classical muscular dystrophy. Since the chemical structure of carnitine is similar to that of betaine, its role as a potential methyl donor in the formation of creatine will also be discussed.

Direct Electro-Titrimetric Measurements of Water in Blood Based on the Karl Fischer Reaction.

I. Method. *George B. Jerzy Glass and Henry W. Lawendel.** Department of Medicine, New York Medical College, Flower and Fifth Avenue Hospitals, New York City.

The cumbersome technic of the direct gravimetric method for measurement of water content after drying in the oven, has resulted in current use of indirect technics, such as determination of hematocrit value, specific gravity or protein content of the serum. These allow only an inferential estimation of the water concentration in body fluids. The method reported here fills the gap existing in this regard in biochemical technics, since it permits one to determine the water concentration in mg./ml. of total blood, plasma, serum, cells, or any other body fluid, directly, with total elimination of weighing. The method is based on Karl Fischer titration with iodine, sulphur dioxide and pyridine in methanol, whereby the end point of titration, which proceeds with magnetic stirring and exclusion of air, is determined electrometrically with the use of magnetic eye and dead point technic. The procedure has been made independent from the instability of Fischer reagents by use of water blanks, which are run as reference standards at the same volume as unknown fluid. With the use of ultramicropipets the method allows the water determinations in 0.05 ml. of blood (capillary, venous or arterial, withdrawn with or without anticoagulants) or any other body fluid. The error of the method is less than 1% between triplicate determinations, and less than 0.6% from the mean of quadruplicate estimations. When water measurements are made in total blood and plasma simultaneously, the water content of cells can be calculated by means of the hematocrit figure. A series of 8–10 measurements, each in duplicate, takes about 4 hours.

Direct Electro-Titrimetric Measurements of Water in Blood Based on the Karl Fischer Reaction. II. Blood Water Tolerance Test and Water Concentration in Blood and Plasma of Normals and Patients with Various Pathologic Conditions. *George B. Jerzy Glass, Linn J. Boyd,** *Maurice Golbey,** *Henry W. Lawendel** *and Eugene H. Frank.** Department of Medicine, New York Medical College, Flower and Fifth Avenue Hospitals, New York City.

Using the above described adaptation of Karl Fischer method for direct determination of water in the blood, the authors obtained preliminary data on the water concentration in 250 bloods of normals and patients with various pathologic conditions. These included instances of excessive hydration or dehydration at various stages of disease and during rehydration or diuretic treatment. To prevent the exposure to humidity in the air, the venous blood was collected under fasting conditions with dry needles directly into vacuumtainers containing predetermined amounts of lithium oxalate. All determinations were done within 36 hours after collection of blood under identical conditions in duplicate or triplicate, with a standard deviation not exceeding 1% between individual determinations. The results were correlated with other clinical and chemical data available on the subjects tested. The normal fasting value of the water concentration in the blood was limited within the narrow range of 83 to 86 Gm. of water per 100 ml. of blood. Under pathologic conditions deviations up to ±7% from these values were observed. The pathologic deviations in the concentration of water in plasma were much less. In a large number of cases the water concentration in the blood was determined at intervals of 10–15 minutes for 1–2 hours following oral administration of 1500 ml. of water, and the "blood water tolerance curve" was determined and plotted. The significance of this curve for evaluation of abnormalities in the water absorption and excretion is discussed, and pathologic deviations in this curve are reported. The "blood water tolerance test" is proposed for the study of the water metabolism, as are other blood tolerance tests used in research and clinical medicine.

Total Body Water and Electrolyte Content of Intact and Hypophysectomized Rats Following Prolonged Pitressin Administration. *W. H. Bergstrom, C. W. Lloyd and Erich Loewy.** State University of New York, College of Medicine, Syracuse. (The work was aided in part by grants from Division of Arthritis and Metabolic Diseases of the National Institutes of Health and from Ciba Pharmaceutical Products, Inc. and The Upjohn Company.)

The present study concerns the sodium, chloride and total body water content of normal and hypophysectomized rats treated with pitressin for 11 to 26 days. The results suggest that absence of the pituitary greatly alters the effect of exogenous pitressin in the rat. Four groups comprising 6 to 8 animals each were used.

Intact rats treated with pitressin (1 mU per day for 11 to 26 days) had diminished serum sodium and chloride concentration as compared to normal controls, but showed no change in the ratio of sodium to chloride in serum or extracellular water. Their body water content was unchanged, as was the ratio of extracellular to intracellular water defined by chloride space calculation.

Hypophysectomized rats similarly treated did not differ, in any respect measured, from hypophysectomized controls. Both of these groups had a significantly greater ratio of chloride space to total body water than did intact pair-fed controls. This presumably indicates a relative diminution of cell mass.

The hypotonicity of intact pitressin-treated rats is not explicable by dilution from water retention alone, since total body water was unchanged. A hypothesis suggested by the available data is that

pitressin may establish a new optimal osmolarity defended by either water retention, electrolyte diuresis, or both. The presence of the pituitary is evidently essential, at least in the rat, for the maintenance of hypotonicity during chronic exogenous pitressin administration.

The Simultaneous Determination of Radiosodium, Radiopotassium, and Radiosulphate Spaces. *B. A. Burrows, G. J. Hine* and J. F. Ross.* Radioisotope Unit, Boston V.A. Hospital and the Evans Memorial, Massachusetts Memorial Hospitals, Boston.

A simple method for the simultaneous determination of radiosodium, radiopotassium, and radiosulfate spaces in human subjects has been developed. Utilizing a well-type, gamma-ray scintillation counter and a pulse-height discriminator, the radiosodium (Na^{24}) and radiopotassium (K^{42}) content of liquid samples can be analyzed independently without chemical separation of the isotopes. After the radioactive decay of the short-lived Na^{24} and K^{42}, the radiosulfate content of the samples can be analyzed. The preparation for beta counting of radiosulfate in serum consists of a 1:1 dilution of serum with 10% trichloracetic acid after the addition of 1 drop of carrier sulfate solution. One cu. ml. of the supernatant is dried on pyrex planchets, with a wafer of lens paper and 1 drop of detergent to insure even distribution.

Using the radiosulfate space as an index of extracellular fluid volume, the total exchangeable sodium can be divided into its extracellular and intracellular portions. Repeated assays of body electrolytes demonstrate not only changes in the external balance of sodium and potassium, but also shifts of sodium and potassium into and out of the cellular compartment.

Volume of Distribution of $S^{32}O_4$, $S^{35}O_4$ and Inulin. *E. Lovell Becker and Henry O. Heinemann* (introduced by *Herbert Gershberg*). Department of Physiology, New York University College of Medicine, New York City.

The volume of distribution of radioactive sulphur has been advocated as a rapid method of determining the extracellular fluid space. A comparison with other means of determining this space seemed advisable before sulfate is used to evaluate changes in extracellular fluid volume in disease. Fasting patients with no evidence of renal or cardiac disease received inulin and sodium sulfate intravenously by a constant infusion technic after an adequate priming dose. Radioactive sulfate with an activity of 100 μc. as 1.5 mg. of sodium sulfate was injected intravenously from a calibrated 1 ml. tuberculin syringe. Blood samples for counting plasma activity and the determination of inulin and sulfate were taken at appropriate time intervals. The volumes of distribution of inulin (V_{in}), $S^{32}O_4$ (V_S^{32}), and $S^{35}O_4$(V_S^{35}) were calculated according to the dilution method. Inulin was determined by the Schreiner modification of the Roe method, $S^{32}O_4$ by a modification of the method of Power and Wakefield, and $S^{35}O_4$ was counted in dried samples of plasma and urine.

The V_S^{32} corrected for urinary excretion averaged 19.0% of body weight (S.D. ± 5.1) in a group of 12 normal patients. The simultaneous V_{in} averaged 20.4% of body weight (S.D. ± 2.7). The coefficient of correlation was 0.34. The V_{in} in 10 patients not receiving sulfate intravenously averaged 16.7% of body weight (S.D. ± 2.8). The V_S^{35} averaged 17.2% of body weight (S.D. ± 2.6) in a group of 22 patients.

During simultaneous studies in 10 patients the V_S^{35}, 20 minutes after injection of the radioactive sulfate, was 17.2 ± 2.6% body weight, while the inulin space amounted to 17.3 ± 2.3% body weight. The coefficient of correlation was 0.3. The ratio of sulfate space to inulin space ranged from 0.65 to 1.48, with a mean of 1.04.

Despite the similarity of the mean value in both series, the actual correlation between the volume of distribution of inulin (V_{in}) and sulfate (both V_S^{32} and V_S^{35}) in any one individual was poor (coefficient of correlation 0.34 and 0.3 respectively). Our results indicate that inulin and sulfate are not always distributed in the same volume of fluid.

A Comparison of Radiosulfate, Chloride, and Sodium Spaces During Acute Changes in Extracellular Fluid Volume. *Richard M. Portwood,* Andrew D. Gwynne* and Donald W. Seldin.* Department of Internal Medicine, Southwestern Medical School of the University of Texas, Dallas.

Although it has been established that ¼–½ of total body chloride is intracellular, it is not clear whether the amount of this nonextracellular chloride involved in changes in extracellular volume remains constant when extracellular volume is changed.

In order to elucidate this point, 9 normal male subjects were studied. In 5 loss of extracellular fluid was induced by thiomerin; in 4 increases were induced by rapid saline infusion. Radiosulfate spaces were measured at the beginning and end of each study; changes in this space were compared to changes in body weight, chloride space, and sodium space. Sodium and chloride spaces were estimated from changes in the balance of these electrolytes and their serum concentrations after assuming that the initial volume of distribution of sodium and chloride was equivalent to the radiosulfate space.

The mean ratios of the calculated changes were: $\Delta wgt./\Delta E_S^{35}$, 0.97 ± 0.26; $\Delta E_{Cl}/\Delta E_S^{35}$, 0.98 ± 0.19; $\Delta E_{Na}+/\Delta E_S^{35}$, 0.93 ± 0.26; $\Delta E_{Na}/\Delta E_{Cl}$; 0.95 ± 0.21.

From a consideration of $\Delta wgt./\Delta E_S^{35}$ it is apparent that radiosulfate is an ideal reference sub-

stance for determining changes in volume of functional extracellular fluid. From $\Delta E_{Cl}/\Delta E_{S}^{35}$ and $\Delta E_{Na}/\Delta E_{S}^{35}$ it appears that only the extracellular portion of total body chloride and sodium is participating in acute changes in balance of salt.

The evidence presented suggests that under conditions of acute losses or gains of saline, only that portion of the total body sodium and chloride participates which is in the functional extracellular fluid as measured by the radiosulfate space.

On Sodium Retention in Edema: An Attempt to Resolve Some Obstacles to Interpretation of Balance Studies. *Gustavo Gordillo* and Jack Metcoff.* Department of Pediatrics, Harvard Medical School and Children's Medical Center, Boston.

A detailed balance study was undertaken in a nephrotic boy, 2 5/12 years, to re-examine the role of sodium in the genesis of edema. Study included consecutive periods of 23, 5, 10, 5, 25 days duration in which 3, 5, 9, 3, 0.5 mM/Kg./day of sodium (NaCl) were given, respectively.

Physiologic adjustment to 3 mM sodium load described regular oscillations requiring 11 days for a complete cycle. Five to nine mM sodium loads produced progressive edema. Reduction of load at maximal weight initiated diuresis with complete loss of edema at the end of observation.

Daily skin losses measured directly averaged 1–2 mM of sodium, potassium, chloride and 2–5 mM nitrogen irrespective of sodium intake. During salt restriction diuresis, skin losses represented 4% of sodium balance; when urinary sodium excretion was reduced by ACTH, they accounted for 80%.

Sodium, chloride and potassium (corrected for nitrogen) retentions of 600, 500 and 300 mM prior to diuresis were twice predicted amounts from increment of weight. Usual calculations of fluid and electrolyte shifts gave inconceivable results. When appropriate corrections for the estimated extracellular phases of skin and skeleton were made before and after diuresis, intracellular potassium content increased markedly, but insignificant changes occurred in intracellular concentrations of sodium and chloride.

This study has three interesting features: (1) the regular cyclic oscillations in sodium balance on a constant intake; (2) the contribution of skin losses to balance; (3) the possible magnitude of retention of salt and water in skin.

Body Sodium and Water in Patients with Heart Disease as Compared to Patients with Hepatic or Renal Disease. *Saul J. Farber and Robert J. Soberman.* Department of Medicine, New York University College of Medicine, New York City.

Edematous states of various syndromes attest to the retention of sodium and water in these diseases. However, the metabolic defects in these conditions are different and so may be their retention and distribution of electrolytes and H_2O. To study the latter abnormality, exchangeable sodium and body water have been investigated in patients with edema due to heart, hepatic or renal disease. The data indicate that edematous patients with heart disease have more Na per L. of body water than do patients with edema due to hepatic or renal disease. Moreover, this finding in patients with heart disease persists after they are clinically edema-free.

Twenty-four hour exchangeable sodium was determined by isotope and body water by antipyrine dilution in 27 normals, 50 patients with edema due to heart disease, 16 cirrhotics, 10 nephritics or nephrotics and 33 patients with heart disease who were previously edematous. In 9 edematous patients with heart disease, body water determined with antipyrine and deuterium were in very close agreement.

The following results expressed as Na, mEq. per L. of body water were obtained: normal, 81; edematous patients: heart disease, 108, liver disease, 90, renal disease, 89; patients with heart disease previously edematous, 100. These groups were statistically different from one another except for hepatic vs. renal disease.

The results show that patients with heart disease as compared to other diseases characterized by Na and H_2O retention are different in their relative Na to water retention and Na distribution. This would indicate a unique metabolic defect in patients with heart disease.

The Relations of Serum Sodium and Erythrocyte Potassium Concentrations. *Harvey C. Knowles, Jr.* and Edward Rubenstein.* Department of Medicine, University of Cincinnati, College of Medicine, Cincinnati.

Studies were made on the relations of serum sodium and erythrocyte potassium levels in conditions of abnormal serum sodium concentration. Thirty-five determinations of sodium and potassium of serum and erythrocytes were made in 14 normal subjects, 3 subjects with primary salt depletion hyponatremia (responsive clinically and chemically to salt therapy), 14 subjects with secondary "adaption" hyponatremia (unresponsive to salt therapy), and 1 subject with hypernatremia. In the normal subjects the mean serum sodium and erythrocyte potassium concentrations were 141 mEq./L. and 96 mEq./L. respectively. In the subjects with adaption hyponatremia the mean serum sodium concentration was 128 mEq./L. (range 118 to 133) and the mean erythrocyte potassium concentration 88 mEq./L. (range 81 to 95). In this latter group the mean erythrocyte potassium concentration was significantly below normal, but the patients presented no clinical evidence of potassium deficiency. In the subjects with depletion hyponatremia the serum sodium concentration ranged as low as 86 mEq./L. In this group the erythrocyte potassium

concentration was in all cases less than 80 mEq./L. In the patient with hypernatremia the serum sodium concentration was 171 mEq./L. and the erythrocyte potassium concentration 115 mEq./L. The plot of all serum sodium and erythrocyte potassium concentrations was linear and highly significant.

It is concluded that: (1) the erythrocyte potassium concentration is related to extracellular fluid tonicity rather than to body potassium content, and (2) the erythrocyte potassium content may be used as a clinical guide to differentiate depletion and adaption hyponatremia.

Serum and Intramuscular Electrolyte Exchanges During Tissue Wastage in Normal and Potassium-Deficient Dogs Following Nephrectomy. *Leonard L. Madison, Donald W. Seldin, and Arthur Grollman.** Departments of Internal Medicine and Experimental Medicine, Southwestern Medical School of the University of Texas, Dallas.

To characterize serum and intramuscular electrolyte exchanges during potassium deficiency and tissue wastage, normal and potassium-deficient dogs (DOCA, high sodium, low potassium diet) were nephrectomized. Serum and muscle were analyzed during control periods, during potassium deficiency and 2 to 9 days following nephrectomy.

Tissue wastage liberated large amounts of potassium and caused profound azotemia in both groups after nephrectomy. In normal dogs, small amounts of potassium (.95 mEq./100 gm. fat free dry tissue/day) penetrated muscle cells, but at the price of severe hyperkalemia which increased in proportion to azotemia ($r = .92$). By contrast, in potassium-deficient dogs, large amounts of potassium (2.27 mEq./100 gm. FFDT/day) selectively entered muscle cells despite hypokalemia. As intramuscular potassium increased (10.9 mEq.), intramuscular sodium decreased by equivalent amounts (10.5 mEq./100 gm./FFDT). The magnitude of intracellular potassium penetration, for each mEq. increment in serum potassium, was 200 times greater in potassium-deficient than in control dogs.

It is concluded that in nephrectomized dogs tissue breakdown liberates large amounts of potassium into the extracellular fluid. If potassium deficiency exists, this potassium is avidly taken up by depleted cells, thereby correcting their deficiency, despite the fact that the profound depression in serum potassium concentration is either unchanged or actually worsened. In normal dogs, the liberated potassium induces severe hyperkalemia; minor amounts of potassium penetrate cells only as serum concentration rises sharply. Finally, this endogenous correction of potassium deficiency following nephrectomy is attended in intracellular exchanges of equivalent amounts of sodium.

Adrenocortical Responsiveness to ACTH in Cushing's Syndrome: Its Possible Relation to the Primary Defect and to the Results of Pituitary Irradiation. *Richmond W. Smith, Jr. and Raymond C. Mellinger.** Division of Endocrinology, Henry Ford Hospital, Detroit.

In patients with Cushing's syndrome, adrenocortical hyperfunction of primary adrenal origin (non-tumor) was postulated to differ in responsiveness to ACTH (endogenous and exogenous) from cortical hyperfunction of primary pituitary origin.

Observations have been made on 5 patients with Cushing's syndrome, 1 of whom had a bilateral upper-temporal visual-field defect. Following 3 days of control study, purified Corticotropin-Gel (Wilson) 1.7 or 3.5 U.S.P. units were given subcutaneously twice daily for 2 days. Of the indices evaluated, the most useful was the increase in urinary 17-hydroxycorticoid excretion per unit of ACTH (2 day total increase in steroid/1000 mg. creatinine/2 day total units of ACTH). This index for 12 normal persons ranged between 0.30 and 1.64 mg. In Cushing's syndrome, the index for the patient with the apparent pituitary lesion was 0.39 mg. and for the remaining 4 patients, from 1.50 to 2.74 mg.

Pituitary irradiation was given to 3 of the 4 patients with increased responsiveness, and to the patient (apparent pituitary lesion) with normal responsiveness to ACTH. Of the former, 1 had a complete remission, and 2 had partial remissions. Although the visual-field defect disappeared in the patient with normal responsiveness, no clinical or laboratory improvement followed comparable irradiation.

These data suggest that in Cushing's syndrome (without adrenal tumor) increased responsiveness to exogenous ACTH may imply (1) that greater decrements of function will follow small reductions in endogenous ACTH and (2) that the degree of responsiveness may help to localize the primary defect and to aid in therapy.

Metabolism of Adrenal Steroids in Dying Patients. *Avery A. Sandberg,* Kristen Eik-Nes,* Leo T. Samuels* and Frank H. Tyler.* Departments of Medicine and Biochemistry, University of Utah, College of Medicine, Salt Lake City.

Adrenocortical function in dying patients has not been well defined. The present study was undertaken, therefore, in order to determine the function of the adrenal cortex and metabolism of 17-hydroxycorticosteroids in moribund patients. The concentration of circulating plasma 17-hydroxycorticosteroids was determined by the method of Nelson and Samuels. The effects of intravenously administered ACTH and hydrocortisone on these levels in dying patients were studied.

Studies in our laboratory have shown that dying is invariably associated with high levels of plasma 17-hydroxycorticosteroids. These levels may

be present for several days before death without known additional precipitating causes. The administration of ACTH *raises* the already elevated 17-hydroxycorticosteroid levels. The rise varied from patient to patient.

To test the role played by impaired metabolism of 17-hydroxycorticosteroids in the production of the high levels in dying patients, hydrocortisone was administered and the rate of disappearance of the steroids from the plasma was followed. In all patients studied there was definite impairment of metabolism of the administered hydrocortisone resulting in the maintenance of very high plasma 17-hydroxycorticosteroid levels. These levels were particularly striking when compared to the rapid clearance of hydrocortisone from the plasma of normal subjects.

We interpret these findings to mean that a factor in the elevated plasma 17-hydroxycorticosteroids seen in dying patients is the impaired metabolism of corticosteroids in the presence of continued production of steroids by the adrenal cortex.

Plasma Clearance of Cortisone and Hydrocortisone in Humans. *Ralph E. Peterson,* Serafim L. Guerra* and James B. Wyngaarden** (introduced by *Franklin G. Ebaugh, Jr.*). National Institute of Arthritis and Metabolic Diseases, and National Heart Institute, Bethesda, Maryland.

Cortisone and hydrocortisone have been administered intravenously to normal subjects, and rates of disappearance from the plasma determined by applying a modification of the method of Silber, using phenylhydrazine-sulfuric acid extraction of methylene chloride extracts of plasma. The steroids were given as 100 or 200 mg. of the crystalline-free alcohol (Merck) in 500 ml. of 5% dextrose in 1.5% ethanol over a 30 minute period. Counter-current distribution studies on the plasma fraction obtained 100 minutes following the end of the infusion have shown that more than 90% of the steroid assayed as the phenylhydrazine is identical with the administered steroid. The biologic half-life for hydrocortisone has shown a mean in normals of 115 minutes. Cortisone disappears from the plasma approximately twice as fast, with a half-time of 65 minutes. In cirrhosis of the liver hydrocortisone disappears at a slower rate than in normals.

Corticosteroid Metabolism in Liver Disease. *Harold Brown, Donald G. Willardson,* Leo T. Samuels* and Frank H. Tyler.* Veterans Administration Hospital and the Departments of Medicine and Biochemistry, University of Utah College of Medicine, Salt Lake City.

The development of technics for the measurement of the 17-hydroxycorticosteroid levels in plasma and urine has made possible a study of the metabolism of these compounds in normal subjects and in patients with liver disease.

After a standard infusion of hydrocortisone in 12 patients with liver disease and in 11 normal subjects, the 17-hydroxycorticosteroids disappeared from the plasma in a logarithmic fashion at a rate which was proportional to the functional capacity of the liver as measured by the degree of BSP retention. In patients with hepatitis, serial studies demonstrated the increased rate of 17-hydroxycorticosteroid removal as the liver function improved.

Tetrahydrocortisone, which has been shown to be the major 17-hydroxycorticoid excreted in the urine, disappeared from the plasma at a much more rapid rate which was independent of liver function.

The rise in the plasma 17-hydroxycorticosteroid levels in response to ACTH stimulation in the patients with liver disease was within normal limits.

The daily urinary excretion of 17-hydroxycorticoids of the patients with liver disease was 3.5 ± .4 mg. as compared with 5.5 ± 1.2 mg. for the normal group. These results differ from those of other workers who used less specific methods for the measurement of adrenocortical steroids.

These data indicate the important role of the liver in corticosteroid metabolism.

The Effects of Carbonic Anhydrase Inhibitor in Addison's Disease. *George J. Hamwi and David B. Brown.** Division of Endocrinology and Metabolism, Department of Medicine, The Ohio State University Health Center, Columbus.

Carbonic anhydrase inhibitor (CAI), Acetazoleamide, was administered to two Addisonian patients in order to determine the possible interrelationships in the kidney between the carbonic anhydrase mechanism and the adrenal cortical hormones in their regulation of the urinary electrolyte excretion.

Each patient was maintained on a constant carbohydrate, fat, protein, and salt intake. Adrenal replacement therapy was withheld for at least 1 week prior to starting the study. Twenty-four hour urines were collected and the urinary volume, pH, specific gravity, sodium, potassium, and chloride was determined. Serum values for sodium, potassium, chloride, and CO_2 combining power were also obtained. The effects of CAI were recorded before and after adrenal hormone replacement therapy was instituted. The adrenal hormones administered were hydrocortisone in 1 period and a combination of DOCA and cortisone in 2 periods.

The administration of CAI resulted in an increase in the urinary volume and the total excretion of sodium, potassium, chloride, and an elevation of the pH before and after treatment with the adrenal steroids. Minor quantitative but no qualitative differences were noted between the effect of Compound F and a combination of DOCA and cortisone after the administration of CAI. These results point to the fact that the carbonic anhydrase mechanism

can operate in the absence of the adrenal hormones. Furthermore, the ion exchange mechanism controlled by the adrenal steroids can operate in the presence of CAI.

Since CAI produced the signs and symptoms of adrenal insufficiency in both patients prior to steroid replacement therapy, the possibility of using CAI as a diagnostic test for Addison's disease is suggested.

It is also postulated that a defect in the carbonic anhydrase mechanism may be a cause of the "salt losing syndrome," since it was shown that the inhibition of carbonic anhydrase produces a diuresis of sodium and chloride independently of adrenal steroid activity.

An in vitro Study of Thyroid Metabolism. A New Thyrotrophin Assay. The Non-Equivalence of all Thyroidal Inorganic Iodine. *John L. Bakke and Nancy Lawrence.** Veterans Administration Hospital and Department of Medicine, University of Washington, Seattle.

Tissue slice experiments lend themselves to hormone assay purposes because the hormone is confined to its target tissue in 1–2 cc. of incubating medium avoiding dilution throughout body fluids as occurs in all in vivo assays. Sixty comparable slices from a single lobe of beef thyroid were incubated in an antibiotic-levulose-phosphate buffer medium at 37° for 0.1–27 hours and the QO_2 determined and the I^{131} turnover measured in the trichloracetic acid soluble and insoluble fractions.

Organic binding of iodine was increased by 8 mU and inorganic iodide collection was stimulated by as little as 0.01 mU of TSH added to the medium. The inorganic iodide was found to be differentially eluted from the tissue by brief serial incubations in saline, thiocyanate, and concentrated iodide solutions. This non-equivalence of the thyroidal inorganic iodide was altered by TSH. These observations suggest that there may be at least 2 serial inorganic iodide compartments anterior to organic binding.

The effects of adenosine, 2–4 dinitrophenol, anoxia, adrenal steroids, ACTH, dextrose, levulose, insulin and cobalt on thyroid metabolism; measurements of dehalogenase activity and thyroxine-triiodothyronine autohormonoclasis will be presented.

The Effect of Thyroid Extract Upon Serum Lipoproteins and Cholesterol. *Beverly Strisower,* John W. Gofman, Elmer Galioni,* Joshua H. Rubinger* and Alexander Simon.** The Donner Laboratory, Division of Medical Physics, University of California, Berkeley, the Stockton State Hospital of the Department of Mental Hygiene, Stockton and the Langley Porter Clinic, Department of Psychiatry, University of California School of Medicine, San Francisco.

An investigation has been made of the effect of graded doses of exogenous thyroid extract upon the entire spectrum of low-density serum lipoproteins. At a dose of 10 gr. of thyroid extract in 11 apparently euthyroid individuals marked lowering of the Standard S_f 0–12 and Standard S_f 12–400 lipoproteins occurred and was maintained during a 10-week period of thyroid administration. At lower doses (3 or 4 gr.) similar lowering of these classes of lipoproteins was observed. In approximately ¼ of the cases studied the lowering was maintained over a 5-month period of study. On this schedule the remaining patients fell into 2 categories: those experiencing marked initial lowering with a subsequent rise to preadministration levels in spite of continuation of thyroid extract, and those who failed to experience any lipoprotein reduction on this dosage schedule. There is a positive correlation between initial lipoprotein level and the magnitude of lipoprotein lowering during thyroid administration. The lipoproteins of higher flotation classes, standard S_f 20–100 and Standard S_f 100–400, were not as regularly influenced by thyroid administration as were the Standard S_f 0–12 and Standard S_f 12–20 lipoproteins. Parallel observations were made in all cases for the serum cholesterol levels.

The Effect of Iodide on the Rate of Release of Hormone from Toxic Thyroid Glands. *Richard E. Goldsmith.* Department of Medicine, Cincinnati General Hospital, Cincinnati.

The effect of iodide ion on the toxic human thyroid gland has been studied for many years. There is evidence showing a decrease in proteolytic enzymes in iodine-treated toxic glands as compared to untreated toxic thyroids. It has also been shown that incubation of TSH with iodide will inactivate the usual stimulating effect of TSH on the iodide uptake of thyroid slices. The present study demonstrates the in vivo effect of iodide ion on the rate of release of radioiodine-labelled hormone from the methyl mercaptoimidazole-blocked thyroids of patients with hyperthyroidism. Nine such patients were studied including controls. The data show that iodide produced a statistically significant slowing of the rate of release of thyroid hormone. When TSH and iodide were administered simultaneously there was a neutralization of the effects on hormone release expected when each is given alone (TSH accelerates and iodide decelerates). The iodide effect is therefore thought to occur by interference with TSH activity.

Kinetics of Protein-Bound Iodine Release and Utilization. *Jean Meszaros* and Robert Robbins.* Temple University Medical School and Hospital, Philadelphia.

Exogenous thyroxin turnover times were measured by injection of Abbott's radio-1-thyroxin; 2 toxic patients had turnover times of 1.5 and 1.8 days,

while 16 euthyroid patients had turnover times of 3.3 to 15 days.

Endogenous thyroxin turnover was also studied. The level of TCA precipitable radioactive PBI in the plasma at any time is subtracted from the maximum level corrected for change in availability from the thyroid, giving a term (ku + ke + kr) representing the difference between utilization and excretion rate and the release rate. This term, measured for 6 toxic patients, ranged from .67 to 1.3 per day, and, for 2 euthyroid patients .32 to .5 per day.

If the observed gland activity is corrected for reutilization by dividing by (1–24 hour gland uptake), the release rate kr is found; this varied from .10 to .32 for the toxic patients, and .04 to .08 for the euthyroid patients. From this and the above the utilization and excretion constants (ku + ke) may be found, ranging from .84 to 1.65 per day for the toxic patients and .35 to .57 for the euthyroid patients. These correspond to thyroxin turnover times of .6 to 1.2 days for toxic and 1.8 to 2.9 days for euthyroid patients. This is considered good agreement with the values obtained from the exogenous thyroxin turnover studies.

The Effect of Prolonged Exposure to Cold on Thyroidal Function in Man. *Sidney H. Ingbar, Charles R. Kleeman,* Murray Quinn* and David E. Bass.** Army Medical Service Graduate School, Washington, D.C., and the Quartermaster Climatic Research Laboratory, Lawrence, Mass.

In animals, exposure to cold results in increased thyroidal function. Attempts to demonstrate comparable effects of cold exposure in man have, however, been inconclusive. The following studies, in which the severity of the cold stress was rigidly controlled, were therefore carried out.

Five normal men, wearing only cotton underwear, lived continuously in a constant-temperature room kept at 27°C. for 21 days, cooled to 13°C. for 12 days, and returned to 27°C. for 13 days. During cold exposure, more rapid loss of thyroidal radioiodine and accelerated appearance of organic I^{131} in plasma indicated a more rapid release of glandular hormone. Thyroidal radioiodide clearance rates increased from a mean of 15.9 ml./min. to 32.6 ml./min. following exposure to cold, and decreased to 21.0 ml./min. during the recovery period. Plasma concentrations of inorganic iodide, calculated from the renal radioiodide clearance rate and the rate of excretion of stable iodine, showed no consistent change. Absolute rates of hormone manufacture, calculated from thyroidal clearance rate and plasma iodide concentration, increased during cold exposure from a mean of 31.2 μg./day to 78.3 μg./day, and returned to 33.6 μg./day during the recovery period. Failure of serially determined PBI's to increase during periods of markedly augmented hormone production indicated that this augmentation represented a response to accelerated hormone utilization.

The data provide evidence in man of the ability of environmental factors to modify bodily requirements for thyroid hormone.

The Amino Acid Pool and the Protein Synthesis Rate in Patients with Primary Myxedema before and after Treatment with *l*-triiodothyronine. *K. R. Crispell, William Parson and Guy F. Hollifield.** Department of Internal Medicine, University of Virginia School of Medicine, Charlottesville.

The urea space, the size of the amino acid pool, and the protein synthesis rate have been determined in 5 healthy volunteers using N^{15} glycine and N^{15} urea by the method of San Pietro and Rittenberg.

The same type of study has been carried out in three patients with primary myxedema. The patients were studied under the usual standard metabolic regime. An interesting but unexplained finding was a moderate degree of positive nitrogen balance determined by classical nitrogen studies. However, the protein synthesis rate as determined by the isotopic nitrogen technic was consistently decreased in the patients with myxedema. The average in the 3 patients was 336 mg./Kg. per 24 hours (range 180 to 480 mg.) as compared to an average of 810 mg./Kg. per 24 hours (range 610 to 1170 mg.) in the 5 healthy volunteers. The size of the amino acid pool was not consistently altered.

In 1 patient the oral administration of 35 μg. of l-triiodothyronine daily for 6 months, with the attainment of the euthyroid state, resulted in an increase of the protein synthesis rate from a pretreatment low of 180 mg./Kg. per 24 hours to a near normal level of 580 mg./Kg. per 24 hours. The other 2 patients are under therapy at the present time.

This type of technic may offer further insight into the metabolic defects of protein metabolism in thyroid dysfunction.

The Metabolic Response to Dihydrotestosterone of 8 Aged Men on High and Low Protein Diets. *Donald M. Watkin, Janis Parsons,* Marvin Yiengst,* and Nathan W. Shock.** Section on Gerontology, National Heart Institute, National Institutes of Health, Bethesda, and Baltimore City Hospitals, Baltimore, Maryland.

The effectiveness of dihydrotestosterone as an anabolic agent in the aged was examined by the intramuscular administration of 25 mg. daily doses to 8 healthy men, aged 70 to 92, during 20-day periods on both high (106 gm. N/day) and low (52 gm. N/day) protein diets in a rigidly controlled metabolic balance study of 5 months duration. The hormone caused retention of N, K and P but a slight loss of Ca at both protein levels. It produced reten-

tion of K in excess of and of P below that predicted from N and Ca balances. It caused greater N, K and P retention on high than on low protein diets. However, the hormone-induced increments in retention on the low protein regime were only half those produced by high protein feeding alone. In the blood, dihydrotestosterone produced a polymorphonuclear leukocytosis, no change in RBC, Hct or Hb, and no change in serum Ca, P, alkaline phosphatase, total protein, albumin or globulin. In the urine it caused a rise in 17-keto- and a slight fall in 11-oxy- and 17-hydroxy-steroids. Its effects on N, K, P and Ca retention and on urinary steroid excretion contrast to those of stilbestrol. Intense local pain, swelling and widespread myalgia developed at the site of administration 8 to 10 hours after injection. Fluid retention led to dependent edema in 6 subjects. Mild euphoria and increased libido appeared. In normal old men, dihydrotestosterone has anabolic properties but is not recommended as a substitute for a high protein diet.

Changes in Body Weight due to Testosterone Proprionate during Restricted Sodium Intake. *E. Raymond Borun, Ernest Geiger and Elizabeth Reisinger.** University of Southern California School of Medicine, Los Angeles.

Previous investigators demonstrated that testosterone proprionate (T.P.) may cause weight gain disproportionate to nitrogen retention, and attributed the excess weight to increased extracellular fluid secondary to sodium retention. The present study shows that weight changes disproportionate to nitrogen retention also occur in the absence of significant sodium retention.

Five male patients with poor nutrition secondary to chronic disease received weighed low sodium diets calculated to contain constant amounts of nitrogen. Two received a salt supplement. Daily observations included body weight, fluid intake, urine volume, and determinations of urine creatinine, nitrogen, and sodium. After adjustment to the diet, a 7–15-day control period was followed by 10 days of T.P. (100 mg. in oil i.m. daily).

Four cases had increased weight gain during T.P. administration. The 2 cases receiving salt supplements had sufficient sodium retention to account for the major portions of the net gains by proportional increases of extracellular fluid. Two of the cases on low sodium intakes had only slight net changes in sodium excretion but showed net weight gains (3.8 Kg. and 1.3 Kg.) 2 and 4 times the amounts expected on the basis of 30 Gm. of retained nitrogen per Kg. of tissue. Positive "water balances" (fluid intake minus urine volume) can account for the weight gains. The 5th case had nitrogen retention (47 Gm.) without increased weight gain.

Balance studies in normal male during low sodium intake also demonstrate that weight change and water retention do not necessarily parallel eigher nitrogen or sodium retaining effects of testosterone proprionate.

Alterations in Serum Lipoprotein Distribution Induced by Gonadal Steroids: Evidence of a Regulatory Role of These Steroids in Protein- Lipid Association. *Robert H. Furman, R. Palmer Howard and Loyal L. Conrad.* Oklahoma Medical Research Foundation and the Department of Medicine, University of Oklahoma School of Medicine, Oklahoma City. (This study was supported in part by research grants from the National Heart Institute (H-1429) and the Smith, Kline and French Foundation.)

The demonstration of estrogen prophylaxis against experimental chick atherosclerosis (Katz), the finding that cholesterol and phospholipid distribution between Cohn plasma fractions I & III and IV, V & VI, (containing beta and alpha lipoproteins) is greatly influenced by gonadal steroids (Barr), the paucity of atherosclerosis in eunuchs (Gertler) and the remarkably lower incidence of atherosclerotic manifestations in the premenopausal female demand clarification of the role gonadal steroids play in atherogenesis and lipoprotein metabolism.

The effect of gonadal steroids was noted in a variety of subjects, utilizing the analytic ultracentrifuge and a solvent density of 1.21 (Lewis), and conventional electrophoresis. Alpha-1, -2, beta and faster floating lipoproteins were studied.

Studies in hypogonadal individuals and in subjects with disturbed pituitary function indicate that in the absence of a physiologically significant androgen effect, alpha-1 lipoprotein increases significantly in both sexes. Methyl testosterone is highly effective in reducing serum alpha-1 lipoprotein concentration several-fold. Conjugated equine estrogens (Premarin) in doses tested do not prevent this reduction. In the normally androgenic male diethyl stilbestrol is effective in increasing serum alpha-1 concentration. Alpha-2 lipoprotein may not change or may vary inversely with alpha-1 concentration changes induced by these steroids. Beta lipoproteins and less dense complexes show more variable responses. Marked steroid-induced lipoprotein changes detected with the ultracentrifuge are not associated with similar changes in globulin patterns as noted by conventional electrophoresis.

The data indicate that gonadal steroids induce changes in lipoprotein distribution by influencing the amount and/or nature of lipid(s) associating with globulins.

GASTROINTESTINAL SYSTEM

Studies on the Electrolyte Content of Human, Mixed, Paraffin-Stimulated Saliva. *Abraham G. White, Paul S. Entmacher,* George Rubin,* and Louis Leiter.** The Medical Division, Montefiore Hospital, New York City and the Department of Medicine, The Mount Sinai Hospital, New York City.

The mean salivary concentration of sodium, potassium and chloride in 73 normal subjects after chewing paraffin for 15 to 20 minutes in the fasting state was found to be: Na, 26.4 ± 11.8; Cl, 29.0 ± 8.8; K, 19.7 ± 3.9 mEq./L. After daily injections of 10 mg. desoxycorticosterone acetate (DCA) in oil for 5 to 15 days into 19 subjects there was a decrease of 3.8 mEq./L. of sodium ($p = .14$), a decrease of 5.9 mEq./L. of chloride ($p = .0002$), and an increase in potassium of 1.81 mEq./L. ($p = .0008$). These figures approach those of sodium and chloride in the saliva of patients with congestive heart failure (Na = 17.8 ± 8.9, Cl = 22.2 ± 8.4 mEq./L.), but the potassium did not reach the high concentrations observed in the cardiac patients (K = 24.7 ± 4.8 mEq./L.). DCA did not affect the salivary Na/K ratios in a statistically significant fashion. The salivary concentrations of sodium, chloride and potassium following DCA treatment were the same as those reported previously by us for normal subjects on a salt-free diet. Pilocarpine, 6 mg. administered subcutaneously, increased the salivary concentration of sodium by 4.11 mEq./L. ($p = .069$), lowered the chloride by 2.42 mEq./L. ($p = .065$) and lowered the potassium by 3.97 mEq./L. ($p = .0001$). Two cc. of mercuhydrin, administered to 10 patients with congestive heart failure, had no statistically significant effect on the salivary concentrations of sodium, chloride or potassium, 1½, 3 and 24 hours following the injection of the diuretic. Attention is drawn to the hypotonicity of saliva (secreted by a gland of ectodermal origin) in contrast to the approximate isotonicity of the other gastrointestinal secretions (derived from glands of endodermal origin). This poses the problem of the relationship between the electrolyte concentrations of secretions and the embryologic derivation of the corresponding glands.

Roentgen Studies of Esophageal Transport in Patients with Dysphagia Due to Abnormal Motor Function. *Stanley H. Lorber and Harry Shay.* Samuel S. Fels Research Institute, Temple University School of Medicine, Philadelphia.

Roentgen studies of esophageal transport were obtained in 38 patients whose chief complaint was dysphagia and in whom no organic obstruction of the esophagus existed. With the patient sitting, 15 cc. of a barium-water mixture were administered orally and esophageal emptying was carefully timed. If emptying was incomplete in 3 minutes, esophageal retention was estimated. Similar observations were made after the consecutive subcutaneous administration of 5 mg. of Urecholine and 30 mg. of Dibuline, each study being performed at the height of drug activity. Each part of the study was repeated 3 times and, in addition, other drugs were investigated.

From the results of parasympathetic stimulation or depression one can divide these patients itno 2 groups.

A. In 16 patients, diagnosed as having chronic cardiospasm, administration of Urecholine produced severe spasm of the lower esophagus similar to that induced by Mecholyl. Vomiting and substernal discomfort occurred in most. Administration of the parasympathetic depressant Dibuline not only relieved the Urecholine induced spasm but was followed, in most, by an increase in esophageal transport over that of the control period. Nitroglycerin (0.4 mg.) administered sublingually was the most effective drug in producing esophageal evacuation.

B. In the remaining 22 patients, esophageal transport remained the same (6) or improved (16) after Urecholine administration but decreased after the administration of Dibuline. Patients in this group had the following diagnoses: Congenitally shortened esophagus with hiatal hernia, constriction ring of esophagus, esophagitis and normal esophagus.

The physiologic, diagnostic and therapeutic implications of these observations are stressed.

The Electrolyte Composition of Human Gastric Secretion. *John A. McGowan and Malcolm M. Stanley.* New England Center Hospital and Tufts College Medical School, Boston.

In order to obtain information about the origin of the various components of gastric juice the secretion pattern of the major electrolytes was studied in 12 subjects, including those with peptic ulcer, gastritis, hypokalemia and hypocalcemia, metabolic alkalosis and respiratory acidosis.

In unstimulated secretions the following approximate range of values was observed: H^+ 0–65 mEq./L.; Cl^-, 80–152 mEq./L.; Na^+, 20–90 mEq./L.; K^+, 5–19 mEq./L.; Ca^{++}, 0.6–2.0 mEq./L. In resting and histamine- and caffeine-stimulated juices there was a reciprocal relationship between H^+ and Na^+. With a rise in H^+ concentration K^+ also increased, although not proportionately. With concentrations of H^+ greater than 90 mEq./L. values of Na^+ as low as 10 mEq./L., and of K^+ as high as 19 mEq./L., were found. Thus, in some instances the K^+ concentration exceeded that of the Na^+. In anacid specimens the concentrations of K^+ varied from 10.4 to 19 mEq./L., and of Cl^- from 77 to 103 mEq./L.

K^+ and Cl^- occur in gastric secretion in the absence of H^+, hence are probably in part secreted by other than parietal cells. Na^+ appears to be secreted entirely from nonparietal cell sources. The apparent direct relationship between increases in concentrations of H^+, and of K^+ above the anacid basal concentration, suggests that at least part of the latter may be secreted by the parietal cells. Another possibility is that part of the K^+ may arise from lysed epithelial cells, the desquamation and digestion of which would be accelerated nonspecifically by the stimulation of acid secretion.

A Method for Measuring the Reservoir Function of the Gall Bladder. *Joseph M. Gambescia** (introduced by *Harry Goldberg*). Department of Gastroenterology, Hahnemann Medical College and Hospital, Philadelphia.

The gall bladder functions not only as an organ for concentrating bile but also as a reservoir for hepatic bile. Cholecystography measures concentrating function but no method has been available to study reservoir function. A method is presented which measures the reservoir function of the gall bladder and in addition reflects the patency of the extra hepatic biliary tree.

There is a constant output of hepatic bile into the duodenum. This output may be altered following the use of hydrocholeretic, and the direction of alteration reflects the presence or absence of a diseased gall bladder and the presence or absence of common duct obstruction.

The method essentially is the use of biliary drainage in which, in unit time, the volume and icterus index of the duodenal aspirate are measured before and after the intravenous injection of sodium dehydrocholate (a hydrocholeretic). This procedure has been applied to 123 individuals with suspected biliary tract disease. Fifty of these to date have been proved by surgery or at autopsy. The procedure in these cases was in error on 3 cases. The procedure applied to 74 other individuals has revealed results substantiated by laboratory findings and the clinical course in 72.

The results of the procedure indicate that it may be of particular value in determining the patency of the common duct in the presence or absence of jaundice. Typical cases will be presented.

Use of the Resistance Wire Strain Gage for Measuring Gastrointestinal Pressure and Motility: Presentation of a New Method. *Vince Moseley, Roy A. Howell, Jr.** *and Oliver J. Brody.** The Department of Medicine of the Medical College of South Carolina, Charleston.

The purpose of this presentation is to describe a new method for measuring intraluminal gastrointestinal pressures and motility. We have constructed a pressure transducer, utilizing the principle of the resistance wire strain gage, which can be used to make direct measurements within the lumen of the gastrointestinal tract. It obviates many of the difficulties encountered with the balloon and open-tube technics now in use. It has the added advantage of being inexpensive and simple to construct and operate.

Our instrument consists of a fiber cylinder 20 mm. long and 5 mm. in diameter, around the surface of which 1 mil strain gage wire is suspended. Insulated wires lead from this to a Bush Strain gage analyzer and ink writing oscillograph recorder. The gage is protected by a small rubber membrane covering. Pressure on the rubber membrane from any direction will change the tension on the strain gage wire stretched beneath it and the change in resistance so produced on a balanced Wheatstone bridge can be measured electrically by an analyzer and recorded by an ink-writing oscillograph.

Slides have been prepared to illustrate some of our observations with this instrument: the sensitivity of the instrument as demonstrated by variations in water pressure; the type of recordings that can be made from the esophagus, stomach, duodenum and colon of a normal individual; similar tracings obtained from patients with peptic ulcer and irritable colon syndrome; and, finally, the response of the stomach and colon to administration of an antispasmodic drug (tricyclamol).

Motility Patterns in the Upper Small Bowel in Healthy Persons and Patients with Duodenal Ulcer or Ulcerative Colitis. *William F. Foulk, Jr.,** *Charles F. Code, J. Arnold Bargen** *and Carl G. Morlock.** Mayo Clinic and Mayo Foundation, Rochester, Minnesota.

This study was undertaken to determine whether the motility, as recorded by a balloon-photokymographic method, in the upper small bowel of healthy persons displays a definite pattern, and if so, whether this differs from that observed in patients with duodenal ulcer or ulcerative colitis. Analysis revealed that the records were composed of small, rapid waves (type I) and slower undulations of the base-line pressure (type III waves).

In healthy subjects fasted 5 to 12 hours, activity of some sort was present 62% of the time. Most of this activity was attributable to type I waves, and 97% of them occurred in a nonrhythmic pattern. Rhythmic type I wave activity was a rare occurrence; it appeared in only 1.7% of 2,650 minutes of tracing obtained from the healthy persons. The frequency of the waves during this rare type of rhythmic activity was fixed at almost exactly 11 per minute. It has been designated as "basic rhythm."

Prolonged fasting in the healthy group resulted in a 50% diminution in total activity and a marked decrease in tone waves (type III), but did not affect the incidence or rate of the basic rhythm.

Five patients with duodenal ulcer showed a suggestive but not statistically significant increase in total motility of the upper small bowel.

Five patients with chronic ulcerative colitis showed a significant increase in the incidence of rhythmic type I waves (basic rhythm). Two of these patients showed a marked diminution of type III or tone waves.

INFECTIOUS DISEASES—ANTIBIOTICS

The Response to Smallpox Vaccination in U. S. Military Recruits. *Sung J. Liao.* The Section of Preventive Medicine, Yale University School of Medicine, New Haven, Connecticut. (Representing part of the work done under the Commission on Virus and Rickettsial Diseases at the suggestion of an *ad hoc* "Committee on Epidemiological Survey" of the Armed Forces Epidemiology Board.)

Though smallpox cases are practically nonexistent in this country, the possible occurrence of an epidemic (however remote) should not be dismissed. The wide variations of the State vaccination regulations and the possible importation of undiagnosed cases from abroad, indicate that a review of the immunologic status of the population is pertinent. Information on the present situation is definitely needed. It is therefore our purpose to present our findings of the response to smallpox vaccinations in U. S. military recruits as of 1951 during an Immunity Survey made at that time.

Among 2682 male recruits (mainly between the ages of 17 and 22 years) 258 individuals (almost 10%) had never been vaccinated before drafted. Among the recruits who were vaccinated after entering the Armed Forces, 2263 gave a definite history as to whether or not they had been previously vaccinated and when. Of this group, 415 (or 18%) showed a "primary" reaction to vaccination. Almost 12% of these "primary reactors" had been vaccinated at one time or another before entering the Services. On the other hand, only 85% of those (206 in number) who had never been vaccinated gave a "primary" reaction, and the other 15% gave either a "vaccinoid" or an "immediate" reaction.

When the geographic regions of this country (from where the recruits came) were taken into consideration, the proportion of the "primary" reaction was similar in the North (18.9%) as in the South (18.3%). However, there were significantly more "primary" reactors among the rural recruits (22.4%) than among the urban (14.7%). These could be possibly explained by the facts, viz.: 1) the proportion of the individuals who had not been previously vaccinated were similar in the North (8.7%) as in the South (9.3%) but (2) more of these same individuals came from the rural areas (14.2%) than from the urban (4.8%).

Because this disease is extremely uncommon in this country the results reflected most probaby the potency of the vaccine lymph employed, the technic of the vaccination performed and the frequency with which it was done at various ages and at various localities in this country.

Finally, these findings indicated the possible extent of the mass immunity to smallpox of a military population group who had a greater risk of exposure to such an infection abroad.

Carriers of Staphylococci among Hospital Personnel. *Mark H. Lepper, Harry F. Dowling and George Gee Jackson.* Department of Medicine, University of Illinois College of Medicine, Chicago.

Because of the importance of staphylococcal carriers among the personnel caring for patients, characteristics of this carrier state have been studied. Nose cultures have been made every 1 to 2 months on each person and the staphylococci isolated. Four personnel have been observed more than 24 months, 17 others more than 18 months, 45 others more than 12 months, 39 others more than 6 months and 46 others less than 6 months. On each subject there has been at least 2 and on 1 as many as 18 cultures taken during the period of observation. One of the striking features has been the tremendous variation in occurrence of positive cultures in different individuals.

The personnel were divided into 3 groups: (1) Initial culture was negative, 57 subjects, 38%, (2) Initial culture positive for coagulase negative organisms, 59 subjects, 39%, (3) Initial culture positive for coagulase positive organisms, 35 subjects, 23%.

Study of the subsequent cultures in these groups revealed the following: Among 386 follow-up cultures of Group 1, 34% were positive (9.5% coagulase positive and 24.5% coagulase negative); among 252 follow-up cultures on Group 2 subjects, 49% were positive (5.5% coagulase positive and 43.5% coagulase negative); among 254 subsequent cultures on Group 3 subjects, 61% were positive (41% coagulase positive and 52% coagulase negative). Thus, Group 3 had significantly more positive follow-up cultures than either Group 2 or Group 1 (X^{-2} 44.2 and 6.7 respectively) and Group 2 had a significantly higher incidence than Group 1 (X^{-2} 15.7). Moreover, Group 3 had a higher percentage of coagulase positive organisms on follow-up culture than Group 2 or Group 1 (X^{-2} 41.3 and 13.2 respectively) and Group 1 had significantly more than Group 2 (X^{-2} 10.4), and the inverse was true for coagulase negative organisms.

It is clear, therefore, that 18% of the subjects were most dangerous as carriers of coagulase positive staphylococci over a prolonged period of time.

Some Epidemiologic Aspects of Toxoplasmosis. *Harry A. Feldman and Louise T. Miller.** Department of Medicine, State University of New York, Upstate Medical Center at Syracuse. (Aided by a grant from the National Institutes of Health, Bethesda, Maryland.)

Information concerning the frequency of antibodies for toxoplasma among normal populations has hitherto been quite inadequate. Utilizing the dye test for determining antibodies for toxoplasma, we have studied 9 normal populations, including those of Iceland and Tahiti; 4 major American cities and the Navajo Indians of Arizona. The variations in over all frequency of antibodies varied from 4% among the Navajos to almost 70% among Tahitians. Antibodies were detected with equal frequency in both sexes. Analysis of 62 cases of congenital toxoplasmosis indicates that infection may be acquired in any season. Studies of fathers and mothers of families in which congenital toxoplasmosis has occurred demonstrate that evidence for infection among fathers is frequently lacking.

Thus, it appears that the frequency of toxoplasma infection varies considerably in different areas, that human to human transfer is unlikely, and that both sexes are exposed with equal frequency. The source of infection, therefore, appears to be in the domicile. On the basis of similar surveys conducted among various animal species, the cat and dog may represent the important reservoirs of human infection.

Laboratory Infection with Histoplasma Capsulatum. *Helen A. Dickie and Marion E. Murphy.** University of Wisconsin, University Hospitals, Madison.

Accidental laboratory infection with histoplasma capsulatum apparently occurred in a group of 17 student medical technicians. Although a causative agent has not been recovered from any of the group, the skin sensitivity and complement fixation studies give very strong support to the belief that infection has occurred.

The group was exposed in February, 1953. Only 1 student had any symptoms and this was a transient grippe-like illness which occurred about 2 weeks after the exposure. The entire group of 17 had routine chest roentgenograms in March, 1953. Of the 17 only the above mentioned student showed any abnormality. A minimal hilar adenopathy which persisted for about 1 month was noted. In May, 1953 this same student developed erythema nodosa. At this time histoplasmin skin testing was done and found to be positive. The history of laboratory work with the fungus was obtained, and the entire class was then studied.

The histoplasmin tests were positive in the entire group. In this area a sensitivity level of about 10% is expected. The complement fixation tests revealed 5 to be positive and 4 suspicious. Subsequent complement fixation tests have shown some variations with a few becoming positive or suspicious in the originally negative group of 7 students. To date, no evidence of clinical disease has been observed.

Histoplasma capsulatum infection may occur from laboratory exposure. Clinical evidence of the infection is minimal. As seen in *Coccidioides immitis* infection the serologic tests are frequently positive subsequent to primary infection without any significant clinical evidence of the disease. Erythema nodosa may be associated with histoplasma capsulatum infection.

The Symptom Complex of Nondysenteric Intestinal Amebiasis. *R. O. Oseasohn, B. T. Garfinkel,* A. S. Benenson.* United States Army, Tropical Research Medical Laboratory, San Juan, Puerto Rico.

The significance of nondysenteric amebiasis remains obscure. Prolonged controlled observations in the natural history of this condition have been conducted in an institutional environment in Puerto Rico.

A group of 25 male adults was selected whose feces were *E. histolytica* positive; an equivalent number of controls were selected. Each week, current symptoms were tabulated and stools were examined bacteriologically and parasitologically. In the event of any symptoms in the intervening period, the subjects were seen immediately and indicated studies performed.

Twenty-one of 25 *E. histolytica* positive patients (84%) passed motile trophozoites at some time during the study, as well as cysts. All individuals originally selected as positive, remained positive during the remainder of the study. Three of 27 who were originally negative became positive subsequently and were transferred to the positive group.

No enteric pathogenes were isolated during a total of 1023 man-weeks of observation. No difference in intercurrent gastrointestinal illnesses was apparent in the 2 groups. Flatulence was more frequent in the *E. histolytica* positive group; anorexia, vomiting and mucus in the stools were more marked in the controls.

This controlled study showed no significant morbidity in adult Puerto Rican males which could be attributed to *E. histolytica*, despite the frequent presence of trophozoites.

Etiology of Secondary Bronchopneumonia in Paralyzed Patients with Tracheotomies. *Mark H. Lepper, Paul Szanto,* Sidney Kofman,* George Gee Jackson and Harry F. Dowling.* Department

of Medicine, University of Illinois College of Medicine, Chicago.

Pulmonary infections are frequent in patients with paralysis of respiratory muscles caused by poliomyelitis. The etiology of these infections, correlated with the histologic findings among fatal cases, was determined in this study. Specimens for culture were taken from the tracheobronchial tree at the time of tracheotomy and every 3 days thereafter. Cultures were taken from several portions of each lobe of the lungs at autopsy, and multiple histologic sections were made from adjacent tissue. The specimens were cultured on blood, chocolate, eosin-methylene blue and Sabouraud's agar plates and in thioglycolate broth. Evaluation of the extent of pneumonia was made by the pathologist without knowledge of the outcome of the bacteriologic studies before correlations were made.

Among 24 patients on whom postmortem examinations were done, atelectasis was an almost constant and usually extensive feature that had no correlation with bacteriologic findings. Ten % of the lobes had evidence of pneumonia without positive cultures. When *Micrococcus pyogenes* var. *aureus* or *Aerobacter aerogenes* was isolated in pure culture, pneumonia was found in 38% and 56% respectively. When mixed flora was found, the incidence of pneumonia was 63%. All of these rates are significantly higher than the uninfected group. Other species found in the infected lungs were enterococci, *Ps. aeruginosa*, *Proteus vulgaris*, *Escherichia coli* and *Candida*. In 70% of patients the strain of microorganism found in the lung parenchyma appeared to be identical with a strain previously isolated from the respiratory tract. Organisms of the same species were also found in the bronchial lymph nodes and several days antemortem in blood cultures.

The Treatment with Erythromycin of 132 Patients with Bacterial Pneumonia. *Monroe J. Romansky, J. P. Nasou* and R. E. Ritts.* George Washington University Medical Division, District of Columbia General Hospital, Washington, D. C.

One hundred thirty-two patients have been studied for evaluation of the effectiveness of erythromycin in bacterial pneumonias. Patients with clinical, radiographic, and laboratory evidence of pneumonia were treated with this agent without selection.

The ratio of lobar to bronchopneumonia was 3 to 1. The organism was identified by blood culture, sputum culture or smear as pneumococcus in 44% of the cases and other organisms were identified in 3% of the patients. Erythromycin was used orally in doses of 100 to 400 mg. every 3, 4, or 6 hours. The total dose was 1 to 5 Gm. for 24%, 6 to 10 Gm. for 26%, 11 to 15 Gm. for 25%, and over 15 Gm. for 25% of the patients. Fever subsided in 57% of the patients within 48 hours of the initiation of treatment. The fever in the majority of the remaining patients had subsided by 72 hours. Nineteen % of the patients were treated for 5 days, and an additional 25% for 7 days, treatment being completed in 70% of the patients within 10 days.

Satisfactory resolution occurred in 96% of the patients, and there was delayed resolution in 1 case. There were 4 deaths; 2 complicated by delirium tremens, 1 from pulmonary infarction following successful resolution of the pneumonia, and 1 from pneumonia due to Friedlander's Bacillus. In this group of patients 1 had pleural effusion with subsequent resorption. Empyema did not occur in this series. Toleration of the erythromycin was good and no gross side reactions were noted.

In vitro sensitivity tests done on 91 strains of pneumococci reveal 76% sensitive to less than 0.1 μg. of erythromycin per ml., 20% sensitive to 0.2 μg. per ml., 3% sensitive to 0.3 μg. per ml. and 1% sensitive to 0.4 μg. per ml.

In this series of 132 patients with bacterial pneumonia treated with erythromycin, the results *appear* to be comparable to those obtained with other antibiotics.

Streptomycin and Isoniazid—In Vitro and In Vivo Evidence for Synergistic Action Against the Tubercle Bacillus. *Monroe J. Romansky, Sol Katz* and E. E. Marshall, Jr.** George Washington University Tuberculosis Research Laboratory, District of Columbia General Hospital, Washington, D. C. (Aided by a grant from the Lasdon Foundation.)

This study was undertaken to determine whether or not streptomycin and Isoniazid exhibit a synergistic action in suppressing the development of resistance of the tubercle bacillus.

In the first part of this study several strains of tubercle bacilli sensitive to streptomycin and Isoniazid alone were passed by repeated transfer (utilizing liquid and solid media) through increasing concentrations of the individual agents. The same parent strains were then passed through increasing concentrations of a combination of streptomycin and Isoniazid.

The second part of this study involved the inoculation of groups of guinea pigs with virulent tubercle bacilli resistant to 30 μg./ml. of streptomycin and Isoniazid respectively, but sensitive to 3 μg./ml. of streptomycin and 0.06 μg./ml. of Isoniazid when they were in combination. These groups of guinea pigs were then treated with streptomycin alone, Isoniazid alone, and a smaller amount of each given simultaneously.

PART I. *In Vitro Results:* Tubercle bacilli became resistant to: (1) streptomycin 10 μg./ml. in 21 days, and (2) Isoniazid 5 μg./ml. in 14 days. On exposure to combination of streptomycin and Isoniazid, became resistant to: (1) streptomycin 10 μg./ml.—required 75 to 125 days, and (2)

Isoniazid 3.0 μg./ml.—required 240 days (maximum resistance that could be produced).

PART II. *In Vivo Results:* Guinea pigs treated with streptomycin alone and Isoniazid alone: Approximately the same amount of advanced tuberculous disease. Guinea pigs treated with streptomycin and Isoniazid in combination: Minimal tuberculous disease (despite resistance of the tubercle bacilli to these individual agents). Autopsy: organisms recovered showed: (1) Same resistance to streptomycin and Isoniazid alone, and (2) Same sensitivity to the combination.

Conclusions: (1) These studies strongly indicate that streptomycin and Isoniazid in combination exhibit synergistic action against the tubercle bacilli, and (2) Evaluation of resistance of tubercle bacilli to individual agents when 2 agents are used simultaneously may be misleading.

Reversal of the Cortisone Depressing Effect on the Therapeutic Efficacy of Antibiotics. *John H. Heller and Philip B. Cowles.** Section of Medical Physics, Department of Internal Medicine and Physiology and Department of Microbiology, Yale University School of Medicine, New Haven, Connecticut.

The host response to bacteria, virus, fungi and bacterial toxins is known to be depressed by cortisone in experimental animals and man. Cortisone further depresses the therapeutic efficacy of antibiotics.

Using radioactive colloidal chromium phosphate as an indicator of reticulo-endothelial function, it could be shown that this system is severely depressed in cortisone therapy. After determining that Vitamin B_{12} and parenteral choline could reverse the cortisone depression, an investigation was carried out on the combination therapy in infection.

Mice that had been injected with *Klebsiella pneumoniae* were divided into 3 groups. The first was treated with Aureomycin, the second with Aureomycin and cortisone and the third with Aureomycin, cortisone, B_{12} and choline. Five series of 3 groups were run with the dose of Aureomycin as the only variable. Each group contained 25 animals.

It was amply confirmed that cortisone could depress the therapeutic efficacy of antibiotics. In addition, it was evident that this depression could be significantly reversed by the addition of B_{12} and choline. In the most critically sensitive series, the mortality of the cortisone group was 40%, while that of the cortisone-B_{12}-choline group was 12%. These results were considered to be statistically significant by the chi-square test. It is suggested that this type of combination therapy should be tried in various disease entities where cortisone is indicated.

Renal Function Changes Associated with Parenteral Administration of Broad Spectrum Antibiotics. *Norman C. Kramer,** *Margaret McCabe** *and Jeanne C. Bateman.* The George Washington University Cancer Clinic, Washington, D. C. (Aided by grants from Lederle Laboratories Division, American Cynamid Co. and Chas. Pfizer & Co., Inc.)

Azotemia has been observed following parenteral administration of broad spectrum antibiotics but at postmortem studies on humans and dogs no anatomic renal changes which could be attributed to therapy were demonstrable.

The significantly higher blood nonprotein nitrogen levels seen in nephrectomized rats treated with intravenous injections of oxytetracycline and chlortetracycline as compared to that in control animals suggested that the azotemia was extrarenal and probably resulted from tissue catabolism. Since some depression of renal function could not be ruled out, these studies were undertaken to investigate this point.

The effects of large doses of intravenously administered oxytetracycline were evaluated by the clearance technics of Goldring, Chasis and Smith. No measurable effect on renal function could be demonstrated following single doses of 0.5 and 2.0 Gm. of oxytetracycline. However, both GFR and RPF were markedly reduced from pretreatment levels after a total dose of 9.0 Gm. given over a period of 15 days. In a terminal cancer patient with already depressed renal function 7.0 Gm. of oxytetracycline given in 5 days further reduced GRF and RPF.

Preliminary studies on dogs indicate that sublethal doses of oxytetracycline (150 mg./Kg. of body weight) produce marked depression in renal excretion of the test substances used.

KIDNEY AND URINARY TRACT

The Relation of Acid Loads to Ammonia Excretion. *Floyd C. Rector, Jr.,** *John Copenhaver,** *and Donald W. Seldin.* Departments of Internal Medicine and Pharmacology, Southwestern Medical School of the University of Texas, Dallas.

Although acid loads augment ammonia excretion, the tubular mechanism producing this response has not been clearly identified. To elucidate this problem 5 groups of rats were tube-fed standard electrolyte-deficient diets for 14 days. Each experimental group received daily supplements of 2 mEq. NH_4Cl, 6 mEq. NH_4Cl, 6 mEq. NH_4Cl + 6 mEq.

KCl, and 6 mEq. $NaHCO_3$, respectively. Urine was analyzed for pH, titratable acid, and ammonia. The kidneys were analyzed for glutaminase activity.

Urinary ammonia increased in direct proportion to the severity of the acid load, and decreased markedly in the animals receiving $NaHCO_3$. Renal glutaminase activity changed correspondingly:

Group	Glutaminase activity μMNH_3/100 mg. dry kidney/hr.
Control	788 ± 39
2 MEQ. NH_4Cl	1327 ± 102
6 MEQ. NH_4Cl	3230 ± 47
6 MEQ. NH_4Cl + 6 MEQ. KCl	3130 ± 159
6 MEQ. $NaHCO_3$	508 ± 42

The correlation of ammonia excretion with renal glutaminase activity was very high (r = .95); ammonia excretion and urine pH correlated only moderately well (r = .77).

During chronic acidosis, lowered urine pH appears to be of only secondary importance in accelerating ammonia excretion. Acidosis of extracellular fluid cannot be responsible for accelerated ammonia excretion, since rats fed 2 mEq. of acid had normal serum bicarbonates. Intracellular potassium content cannot be the regulatory factor, since correction of potassium deficiency prevented neither increased ammonia secretion nor rising glutaminase activity.

It is suggested that increased ammonia excretion during acid loads is a consequence of increased renal glutaminase activity, possibly resulting from intracellular acidosis.

The Production of Hyperchloremic Acidosis to Restore the Diuretic Effect of Mercurial Agents in Patients with Refractory Edema. *Albert L. Rubin,* Hartwell G. Thompson, Jr.,* Warren S. Braveman* and E. Hugh Luckey.* Cornell Medical Division, Bellevue Hospital Center, New York City, and the Department of Medicine, Cornell University Medical College, New York, N. Y. (Aided by grants from the James Foundation and the United States Public Health Service.)

Experience in our laboratory indicates that most patients with edema who fail to respond to mercurial diuretics have normal plasma electrolyte concentrations. In the study to be reported restoration of responsiveness to mercurial diuretics was accomplished in a series of such patients by the production of a hyperchloremic acidosis.

Patients with intractable edema due to heart or liver disease were selected for study. A stable regime, including the daily administration of a mercurial diuretic, resulted in no diuresis in these patients. Observations were made of fluid balance, plasma pH, and plasma and urine electrolyte concentrations.

Pretreatment with combinations of acetazoleamide, a carbonic anhydrase inhibitor, and ammonium chloride resulted in hyperchloremic acidosis with plasma chloride concentrations as high as 129 mEq. per L. and pH as low as 7.14. There appeared to be no untoward effects of acidosis or hyperchloremia produced in this way. In these patients no significant diuresis occurred during the preparatory period with acetazoleamide and ammonium chloride. After cessation of acetazoleamide administration, in the setting of a hyperchloremic acidosis, mercurial administration consistently resulted in a good diuresis. Acetazoleamide inhibits mercurial diuretic effect when administered simultaneously.

All patients studied responded with diuresis to optimal weight. In this study the optimum situation for restoration of responsiveness to mercurial diuretics was a supernormal plasma chloride level and a low plasma pH. Simultaneous administration of acetazoleamide and ammonium chloride effectively and innocuously produces this setting.

The Effect of Diamox on Electrolytes and Blood Gas Exchange. *Thomas E. Cardillo,* Edward W. Mullin,* J. Howland Auchincloss, Lewis Schiffer* and Richard H. Lyons.* Department of Medicine, Upstate Medical Center, State University of New York, Syracuse, New York.

Twenty-five ambulatory cardiac patients requiring weekly diuretics were studied to compare the diuretic effectiveness of Diamox (a carbonic anhydrase inhibitor) with that of Thiomerin. Half of the group was started on Diamox and a placebo injection while the remaining received Thiomerin and a Diamox placebo. After 4 weeks, the 2 groups were reversed. The mean 48-hour weight loss for each week on varying dosages of each drug was plotted. With progressive amounts of Thiomerin (0.5 cc., 1.0 cc., 1.5 cc., 2.0 cc.) the mean weight losses were 0.25, 0.98, 1.5 and 1.9 pounds respectively. On varying dosages of Diamox (250 mg., 500 mg., 750 mg., 1000 mg.) the mean weight losses were 1.3, 2.3, 2.2 and 2.4 pounds respectively. A linear response was obtained with Thiomerin. On Diamox, a uniform response was seen above the 250 mg. dosage. Three patients developed mild, transient paresthesias of their extremities. A favorable dosage-response curve is described comparing varying dosages of Thiomerin and Diamox with the mean 48-hour weight loss produced by each drug.

Fifteen hospitalized patients were studied for serum and urinary electrolyte changes. Serum sodium, potassium and chloride were unchanged. Serum CO_2 and pH fell slightly. Patients with CO_2 retention had the most striking fall in CO_2. Urinary excretion of sodium and potassium was increased while ammonia and titratable acidity decreased.

A patient with emphysema, cor pulmonale, and fluid retention had significantly lower arterial pCO_2 values and a higher O_2 saturation during each of 3

separate courses of Diamox. Another patient maintained on salt restriction alone showed significant reduction of arterial CO_2 content without a fall in pCO_2 or a rise in O_2 saturation.

This suggests that Diamox exerts an effect on arterial blood gas tensions in the presence of heart failure but has little effect in its absence.

Changes of Renal Function and Acid-Base Balance in Potassium Depletion. *John T. Finkenstaedt,* Alfonso Ruiz-Guinazu,* Louis Moreau,* Robert S. Morrison* and John P. Merrill.* Department of Medicine, Peter Bent Brigham Hospital and Harvard Medical School, Boston.

Potassium depletion was produced in six trained, female dogs (9–12 Kg.) by hemodialysis against a bath normally constituted except for absence of potassium. Seventy to 100 mEq. of potassium were removed in each procedure. Body weight, hematocrit, and other electrolytes were unchanged. Potassium depletion, in this manner, produced marked acidosis, increasing in severity as depletion progressed, with observed changes in the following ranges: (1) serum potassium, 4.5 to 1.0 mEq./L., (2) pH, 7.48 to 7.20, (3) CO_2 content, 28 to 18 mM/L. Typical findings of hypokalemia were observed by ECG. C_{IN}, C_{PAH}, and FF were depressed, but potassium excretion continued at control levels, suggesting renal inability to conserve potassium. Hemodialysis against a normal potassium bath did not produce acidosis, changes in ECG, renal dynamics, or electrolyte excretion.

Potassium was infused to the point of intoxication before and after depletion. In control animals, potassium chloride infusion resulted in prompt and progressive increase in K, Na, and Cl excretion. C_{IN} and C_{PAH} increased without change in FF. In the depleted animals the rise in K, Na, and Cl excretion was delayed 60–160 minutes. C_{IN}, C_{PAH}, and FF increased gradually toward control levels. Acidosis was corrected.

These studies suggest that acute potassium depletion produces an (extracellular) acidosis if other electrolytes are maintained constant. This may be corrected by potassium chloride infusion. Decreased C_{IN}, C_{PAH}, and FF are produced by K depletion and corrected by KCl infusion.

Studies of the Effect of Plasma Volume Alterations upon Water Excretion. *William P. Nelson III, Edward Kessler,* Peter F. Lansing,* and Carmen L. Rosano.** Department of Medicine and Medical Research Laboratory, Albany V. A. Hospital, Albany, New York.

Since increases in plasma volume in normal subjects normally hydrated cause increased water diuresis, similar studies were undertaken in 2 patients with diabetes insipidus, and in several normal subjects in a state of physiologic diabetes insipidus. Hematocrit and hemoglobin levels, serum and urine electrolytes and creatinine clearances were determined.

Both patients with diabetes insipidus, normally hydrated, failed to demonstrate any alteration in urine flow following plasma volume expansion with intravenous hyperoncotic salt-poor human albumin. In 1 patient isotonic saline alone, or isoncotic albumin in either saline or glucose solution as vehicle failed to increase water diuresis. While receiving pitressin just sufficient to maintain low urine flow (100 mU each hour intravenously), isoncotic albumin in either saline or glucose solution again failed to augment urine flow. In the other patient, saline or albumin in saline increased urine flow, which, however, was always accompanied by increased quantity and concentration of electrolytes.

Plasma or blood volume expansion, or moderate blood volume reduction, in normal subjects under conditions of physiologic diabetes insipidus, did not influence the high rate of water diuresis.

The results suggest that: (1) the receptor which increases water diuresis following an increase in plasma volume during normal hydration resides in the intact supra-optico-hypophyseal system, (2) this increased water diuresis is due to further suppression in secretion, not inactivation, of antidiuretic hormone, (3) in the overhydrated normal subject, hypotonicity and adequate plasma volume together completely suppress antidiuretic hormone production, and an increase in plasma volume cannot further augment urine flow.

Studies on the Volume Factor in the Regulation of Excretion of Sodium. *Edward Kessler,* William P. Nelson III, Carmen L. Rosano,* and Peter F. Lansing.** Department of Medicine and Medical Research Laboratory, Albany V. A. Hospital, Albany, New York.

Since expansion of the volume of the extracellular space appears to be a stimulus for the excretion of sodium, an investigation to differentiate between plasma and interstitial volumes as the site of this stimulus was undertaken. Hematocrit and hemoglobin levels, serum and urine electrolytes and creatinine clearances were determined.

Plasma volume expansion during high rates of urine flow either in normally hydrated patients with diabetes insipidus, or in water-loaded normal subjects, produced no agumentation in excretion of sodium, provided the vehicle for expansion did not contain sodium. Likewise acute blood volume reduction in 2 water-loaded normal subjects produced no reduction in excretion of sodium for 90 minutes.

A series of studies were then performed in normal subjects during low urine flows, maintained by intermittent intravenous pitressin. 500 ml. of isotonic buffered saline, by expanding interstitial space primarily, increased excretion of sodium markedly. 500 ml. isoncotic albumin in the same saline vehicle, by expanding plasma volume more

and interstitial volume less, resulted in less rapid excretion of sodium. 500 ml. isoncotic albumin in 5% glucose solution, by expanding essentially only plasma volume, resulted in essentially no immediate change, and a late mild increase in excretion of sodium; any fluid loss from intravascular space with this last preparation would pass largely into intracellular space, and would expand interstitial space minimally.

These observations suggest that considerable plasma volume expansion is not a stimulus, while relatively minimal interstitial fluid volume expansion is a definite stimulus to the excretion of sodium.

The Influence of Intraperitoneal Air Injection on Renal Function and Electrolyte Excretion. *Neal S. Bricker and Lloyd J. Gregory, Jr.* Research and Development Branch, Fitzsimons Army Hospital and Department of Medicine, University of Colorado School of Medicine, Denver.

The purpose of this study was to determine the effects of increased intra-abdominal pressure, induced by insufflation of air intraperitoneally, on renal hemodynamics and electrolyte excretion. Ten tuberculous patients without evidence of renal disease or electrolyte abnormalities were studied after 4 months of hospitalization. All drugs were withheld 72 hours before study. An average of 950 cc. of air was delivered and final intraperitoneal pressures averaged 9 cm. of water. PAH clearances (C_{PAH}) and inulin clearances (C_{IN}) were determined for at least 3 clearance periods before and after induction of initial pneumoperitoneum. Excretion rates and corresponding plasma values of Na, Cl, and K were determined during each period.

No significant decrease in C_{in} occurred after pneumoperitoneum. Changes, when noted, were of small magnitude and variable in direction. Decrease in C_{PAH} was somewhat more marked but was significant only in the first experimental period following pneumoperitoneum. Filtration fractions rose in the majority of the patients. Changes in electrolyte excretions were pronounced. Significant decreases occurred in excretion rates of sodium ($P = .01$), chloride ($P = .01$), and potassium ($P = .01$), which persisted even after C_{PAH} returned to normal.

Results of injection of air subcutaneously, of administration of saline into the inferior vena cava during pneumoperitoneum, and of follow-up studies performed after 3 months of weekly pneumoperitoneum will be discussed.

It is concluded that following initial pneumoperitoneum electrolyte excretion decreased abruptly and apparently out of proportion to decrease in renal hemodynamics. Concepts of the mechanisms of this phenomenon will be considered.

On the Mechanism of the Renal Excretion of Iodide: the Influence of Acute Alterations of Glomerular Filtration Rate and NaI Administration on the Renal Clearance of I^{131}. *Neal S. Bricker and Charles J. Hlad, Jr.** Denver, Colorado.

It has previously been shown that the renal clearance of I^{131} ($C_I{}^{131}$) is a linear function of glomerular filtration rate (GFR) in a group plot of patients with stable renal hemodynamics. In the present study, this relationship was examined in individual patients by changing the filtered load of iodide through (1) GFR alterations and (2) elevation of plasma iodide levels.

Acute decreases in inulin clearance (C_{in}) were observed in 5 studies on 4 patients exhibiting transient peripheral vascular collapse during clearance measurements. Under these conditions, $C_I{}^{131}$ decreased out of proportion to C_{in} and consequently clearance ratios ($C_I{}^{131}/C_{in}$) consistently decreased. The return of $C_I{}^{131}$ toward control levels lagged behind that of C_{in}. Conversely, acute increases in C_{in} induced in 6 patients by intravenous aminophylline resulted in elevation of $C_I{}^{131}$ out of proportion to C_{in}, thereby increasing clearance ratios.

Thus, changing filtered load through GFR manipulation resulted in changes in clearance ratios corresponding in magnitude to the degree of GFR alteration, but opposite in direction to that predicted by the group data. When filtered load was increased by intravenous NaI administration (GFR constant), no increase in ratios occurred.

It is concluded that the linearity between $C_I{}^{131}$ and C_{in} characterizing the group is grossly disturbed in the individual when GFR is acutely altered, but not when plasma iodide level is raised.

The relationship of urine flow, other electrolytes, and possible specific aminophylline effects to the observations will be considered. Finally, the contribution of the data to the elucidation of the renal mechanism for iodide excretion will be discussed.

Clinical Value of Percutaneous Kidney Biopsy. *Robert C. Muehrcke,* Robert M. Kark, Conrad L. Pirani* and James A. Schoenberger.* Departments of Medicine and Pathology, University of Illinois College of Medicine, Chicago; Presbyterian Hospital, Chicago; Cook County Hospital, Chicago and The Research and Educational Hospital, University of Illinois, Chicago.

Renal biopsy is a safe and simple procedure of great clinical value in correcting or confirming diagnoses of renal disease, since by its use we can make exact pathologic diagnoses. It is also useful in obtaining cultures of organisms from the kidney; in following the natural history of diseases involving the kidney; in assessing the effects of drugs on renal and cardiovascular disease; and in obtaining data which will help us to understand the physiology and pathophysiology of the kidney. Using a modification of Iverson's technic, in which a renal biopsy is obtained with the patient in the prone position rather than the upright position, a very high percentage

of biopsies are obtained (48 out of the last 50 attempts). This is a distinct improvement on Iverson's technique (Parrish, A. E. and Howe, J. S.: J. Lab. & Clin. Med., *42*: 152, 1953—29 out of 50 attempts). The indications, contraindications, technic, complications, limitations and usefulness of the procedure will be described. In particular, we will describe its value in correcting clinical diagnoses; its usefulness in preventing unnecessary lumbar sympathectomies in patients with hypertension; and its role in serial study of kidney pathology in the progress of lupus erythematosus. Observations on the excretion of P.S.P. by the kidney will also be presented.

A Comparison between Renal Pathology as Seen in Needle Biopsy and Renal Function. *A. E. Parrish, N. Rubinstein,* and J. S. Howe.** Veterans Administration Hospital, District of Columbia General Hospital, and the George Washington University School of Medicine, Washington, D. C.

Renal needle biopsy offers an opportunity to correlate more closely renal pathology with renal function than has previously been possible with autopsied material.

Glomerular function was estimated by measuring inulin clearance, and tubular function by measuring the Tm for sodium para-aminohippurate. These were done by the standard methods of Goldring and Chasis. Biopsy specimens of renal tissue were obtained with a Turkel needle; parafine embedded, sectioned, and stained with hematoxylin-eosin and by the periodic acid method of Schiff. Pathologic changes were graded 0 to 4 –.

Twenty three patients with renal disease ranging from none to terminal uremia were studied in this manner. There was good correlation between glomerular function and structure in 14 instances; and between tubular function and structure in 7 instances. Minor tubular changes such as vacuolization were not reflected in decreased function. However, minor glomerular changes, such as thickening of the basement membrane were reflected in a decrease in the inulin clearance.

There would appear to be, therefore, a fairly good qualitative correlation between renal pathology as seen in needle biopsy specimens and renal function as measured by inulin clearance and TmPAH.

The Effect of a Deficiency of Renal Tissue with or without Resulting Hypertension on the Electrolyte Composition of Brain and Skeletal Muscle. *Louis Tobian, Jr. and John Binion,** Department of Internal Medicine, Southwestern Medical School, Dallas, Texas.

Renal deficiency was produced in a number of rats by removing 1 kidney and compressing the other with a figure-of-eight ligature. Some of these operated rats develop hypertension, others remain normotensive. The electrolyte composition of brain and skeletal muscle was studied.

The operated normotensive rats had an increased potassium content (per 100 Gm. of fat-free dry tissue) in both brain and muscle tissue as well as a decrease in the intracellular sodium of muscle and an increase in the sodium content of brain, compared to normal unoperated rats. These changes were all significant and could not be ascribed to obvious renal insufficiency as measured by BUN, since they were also present in operated normotensive rats without azotemia. These changes were thus related to a loss of renal tissue insufficient to produce any obvious impairment of renal excretory function.

The brain and muscle composition of hypertensive rats was not significantly different from the operated normotensive rats except for a significant 2% decrease in brain potassium content in the hypertensives.

Since renal manipulation in rats without resulting hypertension is associated with changes in tissue composition, the tissue effects of renal hypertension per se can only be ascertained by comparing hypertensive rats with rats that have undergone the same kidney operation but remain normotensive.

These insignificant changes in brain and muscle composition related to hypertension per se are in great contrast to the striking changes in aorta composition that are related to hypertension.

Some Observations on Telescoped Urinary Sediment. *George E. Schreiner.* Department of Medicine, Georgetown University School of Medicine, Washington, D. C.

Krupp, Miale and Cole have described a telescoped urinary sediment as "pathognomonic of visceral angiitis." Addis is quoted as having never observed a telescoped urine in glomerulonephritis. While such emphasis on urinary sediment has been valuable in suspected collagen disease, the term "pathognomonic" deserves critical analysis.

By telescoped urine most investigators mean the association in a single sediment of: (a) red cells, red cell casts and a positive benzidine test (acute glomerulonephritis), (b) significant albuminuria, hyaline casts, cellular casts with vacuoles, oval fat, double refractile fat bodies (nephrotic syndrome), and (c) broad or renal failure casts (chronic glomerulonephritis).

One could construct a theoretic time sequence for glomerulonephritis which would demonstrate just such a sediment. This theoretic patient would have long-standing chronic glomerulonephritis, a nephrotic syndrome supervening late in his disease and an acute exacerbation marking the disappearance of nephrotic edema and the onset of the degenerative, terminal phase. In our experience, such a course of events is not uncommon in the natural history of glomerulonephritis.

The urinary sediments were therefore studied in all available patients with glomerulonephritis admitted to the Georgetown Hospital during 1953. This survey yielded 3 cases demonstrating the characteristic telescoped urine without clinical or laboratory evidence for collagen disease. Autopsy revealed microscopic pathology consistent with classic glomerulonephritis. A brief outline of case histories, slides to illustrate the features of a telescoped urine and photomicrographs of the kidneys will be presented. It is suggested that a telescoped urinary sediment should not per se be considered diagnostic of visceral angiitis.

Diuresis and Changes in Heart Size Following Dextran or Polyvinylpyrrolidone Therapy of Nephrotic Edema. *Lawrence Greenman, Franklin Weigand,* and T. S. Danowski.** Department of Research Medicine, Children's Hospital of Pittsburgh, University of Pittsburgh School of Medicine. (Aided by a grant from the Medical Research and Development Board, Department of the Army, and from Wyeth Laboratories.)

In an attempt to induce diuresis, dextran or polyvinylpyrrolidone in aqueous or saline solution was administered to 18 children hospitalized with nephrosis or with a nephrotic syndrome. Serial measurements of the hematocrit and hemoglobin indicated prompt expansion of the plasma volume which was still marked at 24 hours and which persisted in diminished degree for 5 days following a single infusion of the colloid to 1 of the patients. The anasarca present in 16 of these patients cleared in 12 during diureses induced by these colloids. Facial swelling and pitting edema frequently decreased before a fall in body weight appeared. The 2 additional patients who were not edematous but received dextran had no decrease in body weight.

Serial teleoroentgenograms usually showed a small heart prior to treatment. Definite increases in heart size often followed dextran therapy. These persisted beyond the completion of diuresis.

Our findings indicate that dextran or PVP is an effective agent in inducing diuresis in the nephrotic syndrome of children; the changes in heart size accompanying such therapy presumably reflect expansion of the plasma volume.

ACTH and Cortisone Maintenance Therapy in the Treatment of the Nephrotic Syndrome: Basis and Technic. *Kurt Lange,* Ruth Strang,* Lawrence Slobody* and Eugene J. Wenk** (introduced by *A. Leonard Luhby*). Departments of Medicine and Pediatrics, New York Medical College, New York City.

In the nephrotic syndrome serum complement levels are low, probably as the result of an extensive antigen-antibody reaction. Recent studies demonstrated that excretion of components of complement into the urine could not account for the fall in serum complement because excretion occurred in all severe proteinurias irrespective of the type of disease. In many of the diseases serum complement levels were normal. Perfusion of isolated rat kidneys with nephrotoxic sera, known to produce nephrosis in rats, leads to a marked fall in the complement content of the perfusate. The components of complement removed were the same as those lacking in human cases.

Depression of antibody formation by ACTH or cortisone will effect a rise in serum complement in the nephrotic syndrome. In order to depress antibody formation for a prolonged period, maintenance therapy with ACTH or cortisone was carried out in 21 patients during the last 3 years. Six patients received ACTH. Fifteen individuals were given 400 mg. of oral cortisone on 3 successive days of the week for 6–52 weeks after an initial course of ACTH (100–160 mg./day for 7 days), which had led to diuresis.

The following observations were made concerning maintenance therapy: Maintenance therapy was valuable only when the initial course of ACTH successfully induced complete diuresis. It was advisable to start therapy within a few days after diuresis. High doses of Cortisone had to be given to prevent relapses and only prolonged therapy prevented recurrences secondary to upper respiratory infections. During maintenance therapy proteinuria either disappeared or was markedly reduced and blood chemistries returned to normal. Increased proteinuria was the earliest sign of recurrence of disease and preceded fall in serum complement. Serum complement fell prior to the development of edema.

No untoward effects were observed during therapy and there have been no fatalities. At present all patients are free of edema and protein excretion is absent or low.

The Metabolic Behavior of Patients with Posttraumatic Renal Insufficiency. *Paul E. Teschan, Robert S. Post and Lloyd H. Smith, Jr.* Surgical Research Team, Army Medical Service Graduate School, Washington, D. C.

Because acute renal insufficiency complicating battle wounds resulted in a mortality approximating 90%, a center for its study and treatment equipped with an artificial kidney was established at a forward hospital in Korea. This report includes observations on 51 casualties referred to the Center in 1952.

Initial admission values of NPN as high as 200 mg.% and of potassium as high as 7.5 mEq./L. were recorded by the third post-wound day. Thereafter plasma NPN accumulated at an average rate of 50 mg.%/day while increments of potassium concentration averaged 0.7 mEq./L./day in the

entire series. Occasional daily 100 mg.% increments of NPN and 3.0 mEq./L. increments of potassium concentration were noted. In individual patients, however, the rates of NPN accumulation were only infrequently proportional to those of potassium. Clinical uremia and myocardial potassium intoxication revealed by serial electrocardiograms, progressed with comparable rapidity.

This fulminating course compelled more frequent use of hemodialysis (2.3 dialyses per treated patient) than has been reported for generally non-traumatized individuals (1.6 dialyses per treated patient). Except in moribund patients this procedure dramatically and repeatedly reversed the symptomatic and chemical progression.

The data are presented with interpretations which clarify those clinical and metabolic characteristics of patients with post-traumatic renal insufficiency which differentiate them from non-traumatized patients with acute renal failure. The special importance of hemodialysis in management of these patients is illustrated.

LIVER

Rates of Hepatocellular Plasma Clearance (C_{bsp}) of Infused Bromsulfalein in Normal Ambulatory Men and Women under Standard Conditions. *John W. Eckstein,* Nell K. Levy* and James W. Culvertson.* Cardiovascular Laboratory and Department of Internal Medicine, College of Medicine, State University of Iowa, Iowa City. (Aided by a grant from the Central Scientific Fund of the College of Medicine.)

Because we had shown the standardized plasma clearance rate of Bromsulfalein to be a dynamic and sensitive indicator of hepatocellular function (= plasma flow rate × extraction fraction) in convalescent hospital patients, it became necessary to establish with this study the normal values for healthy ambulatory subjects.

Twenty-five men (aged 22 to 36, mean 28) and 25 women (aged 19 to 53, mean 30) were studied with a constant intravenous infusion of Bromsulfalein at approximately 2.5 mg./min./M.², after an initial priming dose of 50 or 100 mg. After 20 minutes' equilibration serial venous blood samples were drawn through an indwelling needle at 10-minute intervals to the end of the infusion hour. Removal rate (R) is calculated from infusion rate and change (ΔP) in plasma concentration (P). $C_{bsp} = \frac{R}{P}$. Clearance value for each subject represents the mean of 4 observations at standard time intervals, corrected to surface area 1.73 M.².

In men P ranged from 0.48 to 1.28 (mean 0.81) mg./100 ml. and C_{bsp} from 384 to 960 (mean 586, S.D. ±158) ml./min. In women P was 0.51–1.37 (mean 0.92) mg./100 ml. and C_{bsp} 352–836 (mean 531, S.D. ±112) ml./min.

The range of these values is suitable and their frequency distribution good. Findings in patients with liver disease fall into sharp contrast. The method is useful for making absolute estimates of hepatic function and for reflecting changes in blood flow and extraction rates after altered physiologic or pharmacologic conditions.

Liver Function Tests in Patients with Chronic Anemia. *Donald Shotton, Copley McLean,* Myers Hicks,* and Byrd S. Leavell.* Department of Internal Medicine, School of Medicine, University of Virginia, Charlottesville.

This study was undertaken to evaluate the effect of chronic anemia on liver function tests. Ninety-three patients with chronic anemia have been studied. Patients with known liver disease were excluded as far as possible. In addition to determinations of the erythrocytes, hemoglobin and hematocrit, the following tests were employed: Bromsulfalein excretion, cephalin-cholesterol flocculation, thymol turbidity, alkaline phosphatase, total protein, and plasma bilirubin. At least 4 liver function tests were done on each patient.

Fourteen cases of sickle cell anemia were studied. All of the liver function tests were normal except for 1 Bromsulfalein retention of over 5% and 3 serum protein determinations that fell between 6.2 and 5.6 Gm.%. Twenty-seven patients with untreated pernicious anemia were studied. Lowered serum proteins were found in 11. The Bromsulfalein excretion was slightly abnormal in only 3 patients. There were 23 patients with anemia due to chronic blood loss. Five of these had elevated thymol turbidity values and 5 had slight increase in Bromsulfalein retention. Seven patients with hemolytic anemia were studied and all had normal Bromsulfalein excretion. In 10 patients with aplastic anemia and 10 with uremia and anemia only a few abnormal results were found.

In the group of patients with anemia in this study, abnormal liver function tests were not common and only rarely did more than 1 abnormal test occur in the same individual. With the exception of the lowered protein values found in a group of patients with pernicious anemia the results appeared to form no definite pattern. The abnormal results that were observed appeared to be related more to the type of the disease than to the duration or severity of the anemia. From this study it is con-

cluded that chronic anemia per se is rarely a cause of impaired liver function as measured by the usual clinical tests.

The Acid Precipitable Globulin (APG), An Approximation of the Serum Alpha-2 Plus Beta Globulins, in Hepatobiliary Diseases. *Ezra M. Greenspan.* Department of Medicine, The Mount Sinai Hospital, New York City.

A group of globulins designated as "acid precipitable globulin" (APG) was separated and quantified turbidimetrically by diluting 0.1 ml. serum 1:60 with acetate buffer (pH 4.42) at low ionic strength (0.01). APG turbidity was found to be independent of thymol turbidity, or serum albumin, mucoprotein, or protein-bound polysaccharide concentrations. APG was consistently composed of a major moiety of the alpha-2 plus beta globulins. APG turbidity units were not converted into protein concentration equivalents estimated from paper electrophoretic patterns because increased gamma globulin concentrations exerted a limited suppressive effect on APG levels and variable lipoprotein composition of APG resulted in unreliable protein staining factors. However, gross changes in alpha-2 plus beta globulin concentration visualized on paper electrophoresis patterns correlated satisfactorily with APG values except in sera with marked hyperlipemia. The relationship of APG to zinc sulfate (gamma globulin) turbidity values provided a supplementary guide to shifts within the globulin spectrum.

The mean, S.E. and range of APG values among 40 normal adult subjects were: 6.1 ± 0.2(4.1–8.2); in 38 patients with infectious or homologous serum hepatitis, values from the initial serum obtained were 5.9 ± 0.4(2.7–10.7); in 35 patients with portal cirrhosis values were 4.5 ± 0.5(1.7–10.2); in 38 patients with inflammatory or neoplastic obstructive biliary tract disease values were 10.4 ± 0.4(4.7–16.5). The APG/ZnS values among normals were 1.03 ± 0.11(0.6–1.8); among the hepatitis group, 0.67 ± 0.045(0.11–4.3); the cirrhosis group 0.41 ± 0.068(0.06–1.9); the obstructive jaundice group, 2.6 ± 0.23(0.5–10.0).

The application of the APG turbidity to differential diagnosis of hepatobiliary diseases are discussed.

NEOPLASTIC DISEASE

Arrest of Mammary Carcinoma by Cortisone and Hydrocortisone. *Henry M. Lemon and M. M. Davison.** Boston University School of Medicine, Boston.

Contrary to some previous reports, cortisone and hydrocortisone palliate objectively some patients with advanced mammary carcinoma, if administered in adequate dosage and for a sufficient time. This study includes 16 cases observed during the past year, all of whom had become refractory to every other type of hormonal and radiologic therapy, and of whom 5 were considered terminal.

Previous remissions following sex hormone therapy had occurred in several patients receiving marked benefit, suggesting that their cancers were partially hormone dependent. All premenopausal patients had been castrated 3 or more months previously. Symptoms of estrogen withdrawal reappeared or grew worse after several weeks cortisone treatment in 3 patients. The most favorable results were obtained, however, in 10 year postmenopausal patients with intact ovaries.

With maintenance cortisone dosage of at least 100 mg. daily: (1) Regression of lymph node metastases occurred in 2 cases. (2) Osseous recalcification was noted in 3 cases. (3) Hypercalcuria was relieved in 2 cases. (4) Elevated serum acid phosphatase levels decreased toward normal in 10 cases, accompanying other manifestations of improvement, but did not change significantly, or even rose until death, in cases not responding to therapy. (5) Serum alkaline phosphatase increased during osseous repair, declining later to normal (1 case). (6) Gains in body weight of as much as 20 lb., without edema, were noted. (7) Six out of seven nonterminal cases were able to continue nearly normal daily activities, for periods lasting as long as 9 months.

The subjective results of therapy were excellent, and few toxic effects were noted. Hydrocortisone appears as effective as cortisone, but with greater likelihood of inducing edema.

An Abnormal Lipid-like Material and Carbohydrate in the Sera of Patients with Multiple Myeloma. *Bernard A. Sachs, Paxton Cady* and George Ross.** Medical Division, Montefiore Hospital, New York City.

Sera from 11 patients with multiple myeloma were separated by paper electrophoresis and differentially stained for protein, fat and carbohydrate. Of the 11, 7 revealed protein patterns of gamma myeloma and 2 of beta myeloma; 2 were essentially normal.

In 5 of the 7 with gamma myeloma, an abnormal lipid-staining band which migrated with gamma globulin was present. In 1 with beta myeloma and 1 with normal protein pattern, an abnormal lipid band was found between beta and gamma globulin. The other 4 electrophoretic patterns exhibited no lipid abnormalities.

Total lipids, chemically determined, were elevated in only 2 gamma myeloma sera and in 1

with normal protein pattern. These 3 also had increased levels of serum cholesterol and/or lipid phosphorus. In 2 with beta myeloma and 1 with gamma myeloma cholesterol levels were depressed.

Carbohydrate, abnormal in position and increased in amount, was invariably found with abnormal protein whether gamma or beta. This was always associated with an increase in chemically determined total polysaccharides or glucosamine. In 4 sera both these fractions were 2 to 4 times normal. 5 others had a moderate increase in glucosamine; 4 of these had a slight, and 1 no elevation in total polysaccharides. The 2 with normal protein patterns had no abnormal carbohydrate, electrophoretically or chemically.

This increase in serum polysaccharides of patients with multiple myeloma differs from that found by others (Shetlar) in patients with carcinoma in that it is associated with the abnormal globulin rather than albumin.

Use of Triethylenephosphoramide in Malignant Melanoma. *John B. Field.* Department of Medicine, University Southern California School of Medicine and Los Angeles County Hospital, Los Angeles.

It has been reported that triethylenephosphoramide (TEPA) possessed carcinolytic action and actually induced visible improvement in some patients with malignant melanoma. The drug, in oil solution, was given in daily intramuscular injections to the limits of leukopenia. Twenty-four patients were studied from 1 to 10 months. Only 1 had the disease apparently limited to the primary site. This patient, terminal with a mediastinal melanoma with venal caval compression and asphyxiation which were unaffected by a course of intravenous mustards 1 month previously, emerged from coma after 1 week of treatment and was able to leave the hospital 3 weeks later with obvious tumor regression. A second course of treatment after several weeks produced some reduction in symptoms. Palliation lasted about 4 months. One of 2 patients has apparent arrest or inhibition of isolated pulmonary metastases after 10 months, the other had arrest for about 8 months but is now progressing; another had partial regression of some subcutaneous nodules although new nodules appeared during treatment, and 1 patient with proven intracranial metastasis has had arrest of progressive neurologic symptoms and papilledema over 7 months, although skin lesions have been noticeably unaffected. The remaining 19 patients with widespread and parenchymal metastases have had no detectable improvement, the disease advancing at the pretreatment rate. It would appear that therapy with TEPA for palliation might be of some benefit but not when intra-abdominal metastases are present. Studies with TEPA and other chemotherapeutic agents on the Harding-Passey melanoma in mice are in progress and will be reported elsewhere.

NEW SYNDROMES

The Agammaglobulinemia Syndrome in Adult Men. Its Differentiation into Familial Lymphopenic Agammaglobulinemia and Familial Nonlymphopenic Dysglobulinemia. *Irving I. Young* and William Q. Wolfson.* The Unit for Metabolic Research, Department of Medicine, Wayne University College of Medicine and City of Detroit Receiving Hospital, Detroit. (Aided by a grant from the Committee on Scientific Research of the American Medical Association.)

Agammaglobulinemia, not previously reported in adults, is a pathophysiologic syndrome, not a disease; its presence and etiologic type are simply diagnosed and treated by replacement. Four affected men have shown unusually high Howe and true A/G ratios; absent gamma-globulin and low beta-2-globulin, extreme susceptibility to infection; total absence of circulating and fixed antibodies both inherited and acquired (no hemagglutinins, persistent positive Schick and Dick, negative tuberculin); no antibody response to antigenic challenge; negative flocculation tests despite proven liver damage, high fever, and elevated E.S.R. Children studied by Janeway and Bruton and 3 adults have had familial lymphopenic agammaglobulinemia, a sex-linked recessive disorder with clinical manifestations only in homozygous males and no manifestations in heterozygotes. Accompanying deficiency of tissue lymphocytes, absent lymph node germinal centers, and peripheral blood lymphopenia suggest a primary deficiency of tissue lymphocytes. Familial nonlymphopenic dysglobulinemia has been observed in 1 man, whose agammaglobulinemia was not associated with abnormal lymph nodes or blood lymphocytes; relatives of both sexes have shown hypergammaglobulinemia. It may be a disturbance in globulin synthesis by tissue lymphocytes so controlled by multiple alleles that 1 abnormal gene deranges immunoglobulin synthesis and produces hypergammaglobulinemia while 2 abnormal genes render immunoglobulin synthesis impossible. The metabolism of gamma-globulin in these disorders and their differentiation from other hypogammaglobulinemic illnesses will be discussed.

The "Host Factor" in Human Illness: The Occurrence of Differences in General Susceptibility to Illness among a Group of Adult Men. *Lawrence E. Hinkle, Jr. and Norman Plummer.** Department of Medicine, New York Hospital-Cornell Medical Center, New York City.

Because large differences in general susceptibility to illness were found among 1297 adult women, 1527 adult men were studied in the same manner.

The group was homogeneous in economic, social, and cultural background, physical and social environment, occupation, and general exposure to infection. All were well on first observation at age 20 to 25; all had been continuously observed for as long as 35 years; and every illness in each man had been recorded.

28% of the men had 77% of the episodes of illness and 80% of the days of disability during the first year of observation. The distribution was similar in each subsequent year. The group with the highest frequency of illness during the first year continued to have the highest frequency during the whole observation period.

Studies of randomly selected individual men indicate that each frequently ill man had more illnesses in all body systems, more psychologic disturbances, more surgical operations, and more accidents, than a corresponding man in the more healthy group.

High illness rates were more closely correlated with disturbances in body function, mood, thought, and behavior, occurring during attempts to adapt to the social environment, than any other factor. Although disability periods were less frequent and shorter in the men, and the prevalence of various diseases was different, the primary phenomena were the same as those observed in the women. They suggest that disease syndromes are transient aspects of the reaction of the whole individual to his total environment, and that their occurrence is governed as much by the relation of the individual to his social environment as by his random contact with specific etiologic factors.

OBSTETRICS AND GYNECOLOGY

The Importance of Opthalmoscopic Examination and Microscopic Urinalysis in the Classification of Toxemias of Pregnancy. *Frank A. Finnerty.* The Department of Medicine, Georgetown University School of Medicine, and the Georgetown University Medical Division and Georgetown and George Washington Obstetrical Divisions, District of Columbia General Hospital, Washington, D. C.

Serial studies on 318 "toxemia" patients have shown that differentiation between toxemia of pregnancy and hypertensive vascular disease is apparent by examination of the retinae. Regardless of age, blood pressure level, degree of edema or albuminuria, if a generalized retinal sheen is present (a wet glistening appearance of the entire retinae) and the retinal arteries are normal true toxemia exists. If no retinal sheen is present but hypertensive retinopathy is seen, hypertensive vascular disease exists. If both a sheen and hypertensive retinopathy exist, toxemia is superimposed on hypertension. If the opthalmoscopic examination is normal and the arterial blood pressure found to be elevated, early hypertension exists.

Though 95% of the patients referred to the clinic were originally diagnosed as toxemia, only 14% had toxemia by our criteria. Our diagnoses included hypertension (216), hypertension plus superimposed toxemia (28), postpartum hypertension (14), pyelonephritis (15), and toxemia (45).

Fifteen patients masquerading as toxemia with albuminuria and edema were found to have pyelonephritis documented by microscopic urinalysis and urine culture. Therapy with appropriate antibiotics promptly resulted in clearing of the "toxemia."

The ability to differentiate between toxemia and hypertension provided the opportunity to study whether or not toxemia caused vascular damage. Opthalmoscopic examination in 25 of the toxemia group 6 weeks postpartum revealed no abnormality. In 20 patients, however, despite return of the blood pressure to normal and disappearance of edema and albuminuria, examination of the retinae revealed definite retinopathy. These retinal changes are attributed to the duration of the toxemia rather than to its severity.

Measurement of Uterine Blood Flow and Uterine Metabolism with the N^2O Method in Normotensive and Toxemic Pregnancies. *Nicholas S. Assali, R. A. Douglass,* W. W. Baird* and D. B. Nicholson.** Department of Obstetrics, University of Cincinnati, Ohio; Department of Obstetrics and Gynecology, University of California, Los Angeles. (Supported by a grant from U.S.P.H.)

The N_2O method of Kety and Schmidt for the measurement of cerebral blood flow has been adopted for the study of uterine circulation and metabolism in normal and abnormal pregnancies. Uterine venous blood was obtained either by direct catheterization of the uterine vein, via the heart or by cannulation of this vein during abdominal operations. Both technics yielded venous samples, which were representative of the same area. Arterial blood was collected from the brachial artery. Adequate arterial and venous curves were obtained on 7 normal term

pregnancies, 4 with toxemia of pregnancy and 4 normal subjects during the first 24 hours following delivery.

In normal pregnancy at term, the uterine blood flow varied from 12 to 18 cc./100 Gm. of pregnant uterus/min. with an average of 15 cc. Following delivery, the average fell to 9 cc./100 Gm./min. The oxygen consumption during pregnancy varied from 1.4 to 2.4 with an average of 2 cc./100 Gm./min.; the postpartum values averaged 1 cc./100 Gm./min. Uterine vascular resistance during pregnancy varied from 4 to 7 mm.Hg/cc. per 100 Gm. per minute, and rose to an average of 9 in the postpartum period.

In toxemia of pregnancy the uterine blood flow varied from 8 to 12 cc./100 Gm. per minute, the oxygen consumption from 0.8 to 1.5 cc./100 Gm. per minute and the vascular resistance varied from 9 to 12 mm. Hg/cc. per 100 Gm. per minute. In the pregnant subjects, equilibrium between the N_2O tension of venous blood and uterine tissue was achieved only after 30 minutes of N_2O inhalation, whereas in the postpartum period, 10 minutes were sufficient.

These preliminary results suggest that in toxemia the uterine circulation participates in the over-all vasoconstriction which is characteristic of this disease.

PHARMACOLOGY AND THERAPEUTICS

Hemodynamic and Metabolic Changes Induced by Prolonged Administration of Dextran. *John R. Jaenike* and Christine Waterhouse.* Department of Medicine, University of Rochester School of Medicine and Dentistry, Rochester, New York. (Aided by a grant from the United States Public Health Service, National Heart Institute.) Dextran was supplied by Commercial Solvents Corporation.

The use of macromolecular substances as plasma expanders has led to a study of the metabolic and osmotic effects of the polysaccharide dextran in 5 human subjects. Each received 120 Gm. of dextran intravenously, daily for 6 days. Studies were performed on a metabolism ward with a constant low caloric, low carbohydrate diet and suitable control periods before and after dextran administration.

Approximately 70% of the administered dextran was excreted in the urine. Dextran accumulated rapidly in the plasma during the series of injections, reaching a maximum concentration of 2500 to 3500 mg.%.

Each subject showed sparing of nitrogen and phosphorus during dextran administration. With 1 exception, about 130 mg. of nitrogen were spared per Gm. of dextran unaccounted for by urinary excretion or present in the plasma.

All subjects showed an increased plasma and extracellular fluid volume, and diminished total circulating protein during administration. An apparent continued expansion of plasma volume was observed in 2 subjects after dextran was discontinued. This was paralleled by a rise in total circulating protein above control values, which appeared to further expand the plasma volume while dextran concentration was falling. Significant blood levels of dextran and a diminished venous hematocrit were demonstrable for 30 days following administration.

Transient microscopic hematuria occurred in 3 of 5 subjects. GFR, RPF, and TmPAH in 2 subjects remained unchanged.

The data indicate that appreciable dextran is metabolized during the period of administration. Nevertheless, significant amounts remain unchanged in the blood and exert an osmotic effect over a prolonged period of time.

The Clinical Response and Theophylline Blood Levels Noted After Oral Ingestion of Choline Theophyllinate and Aminophylline with or without Aluminum Hydroxide. *Sidney Dann,* John Gagliani,* Arthur C. De Graff* and Herbert S. Kupperman.* New York University-Bellevue Medical Center, New York City.

Comparative study of the clinical tolerance and activity and of theophylline blood levels has been made in patients receiving choline theophyllinate and aminophylline with or without aluminum hydroxide. The clinical effectiveness of choline theophyllinate administered in doses of 200 mg. q.i.d. was studied in patients with bronchial asthma and menstrual molimina. The drug proved to be effective in 40% of the patients with bronchial asthma and produced significant alleviation of symptoms in at least 80% of the patients with menstrual molimina when the preparation was administered 1 week premenstrually. Theophylline blood levels were determined by use of whole blood employing the colorimetric method of Truit et al. Blood was obtained at hourly intervals for 4 hours after administration of a single 800 mg. dose of choline theophyllinate or aminophylline with or without aluminum hydroxide. Comparable theophylline blood and patient tolerance were achieved with the 2 aminophylline preparations. A 20% incidence of gastrointestinal disturbance was noted after ingestion of either 1 of the aminophylline preparations indicating that the addition of aluminum hydroxide did not appear to accentuate or diminish toxicity or affect absorption as measured by blood theophylline levels. Theophylline blood

levels after choline theophyllinate administration were some 60 to 75% higher after the first 2 hours, and 40 to 50% higher 3 to 4 hours after ingestion when compared to levels achieved with the aminophylline preparation. In contrast to the aminophylline drugs, no toxic effects were noted after oral use of comparable doses of the choline theophyllinate preparation.

RESPIRATORY SYSTEM

Evaluation of Circulatory-Respiratory Insufficiency. *William E. Huckabee.** Massachusetts Memorial Hospitals, Boston. (Introduced by *Walter E. Judson*, Boston.) (Reported from Naval Medical Research Institute, Bethesda, Maryland.)

Patients with various degrees of pulmonary dysfunction, veno-arterial shunting of blood or of circulatory failure may occasionally be said to suffer from anoxia. Whether hypoxia is present in the essential sense of tissue deprivation of needed O_2 is a question which is not adequately answered by measurements of alveolar and blood O_2 tensions. It remains difficult to determine whether symptoms or abnormal physiologic measurements are actually due to hypoxia, and whether improvement in such true hypoxia occurs with therapy.

O_2 debt determination, by evaluating the relationship between O_2 supply and demand of the tissues, rather than O_2 supply alone, is an approach to this problem, denoting relative O_2 deficiency regardless of changes in O_2 transport. Difficulties in applying the classical technics preclude their use in forms of suspected hypoxia encountered in pulmonary and cardiac patients. The use of lactic acid production for the indirect calculation of O_2 debt, however, is free of many of these difficulties; because of its relation to hypoxia lactate measurements have been reported for a number of disease states. A more exact evaluation of the relationship between lactate production and O_2 lack is therefore presented.

The animal experiments described reveal a gross lack of correlation between lactate production and O_2 debt under conditions of: (1) exercise, (2) breathing low O_2 gas mixtures, (3) hyperventilation and (4) depression of cardiac output by pressure breathing. A correction, however, is introduced which leads to marked improvement in the correlation between "chemical" and "respiratory" debts. This correction is based upon the total body pyruvate, a quantity which is shown to be acutely variable under several of the conditions studied. The final calculation ("excess lactate") is shown to be closely correlated with true O_2 debt under conditions in which the latter is measurable. Application of this concept to the determination of ml./minute O_2 deficit for the body and for individual organs, and its relationship to blood flows and O_2 contents under the conditions listed is presented. Interpretations in terms of adequacy of circulatory or respiratory function relative to tissue demands are given.

The Relation Between the Rapid Velocity Expiratory Volume and the Maximum Breathing Capacity. *Robert L. Johnson, Jr.,** *William F. Miller** *and Paul L. Richburg** (introduced by *Donald W. Seldin*). Department of Internal Medicine, Southwestern Medical School and the University of Texas, Dallas, and the Cardio-Respiratory Laboratory of the V.A. Hospital, McKinney, Texas.

To establish the relation between velocity air flow and maximum breathing capacity (MBC) the 0.5, 0.75, and 1.0 sec. expiratory volumes (EV) were measured with a modified Gaensler-Collins Vitalometer in 100 normal subjects and 100 patients with pulmonary disease.

The initial component of the expiratory flow curve is approximately a straight line, following which a break occurs, and a second linear component develops. The timed expiratory volumes used in this study fell on this second linear component in both normal subjects and patients with pulmonary disease. The initial linear component, which represents the maximum expiratory velocity, then breaks within the first 0.5 sec.

These findings suggest that the mean expiratory time utilized in performing the MBC should be less than 0.5 sec. This inference is substantiated by analysis of actual tracings (normal subjects 0.33 ± .07 sec.; patients with pulmonary disease 0.38 ± .09 sec.).

A line, the slope of which represents the MBC plotted through zero volume, intersects the second linear component of the expiratory flow curve at a relatively constant time interval in normal subjects (0.56 ± .08 sec.). In abnormal subjects this intersection usually occurred at a greater time interval and was extremely variable.

It is concluded, therefore, that the MBC in diseased states becomes a poor estimate of average maximum expiratory velocity because of undefined variables inherent to the test. The 0.5 sec. expiratory volume, expressed as velocity, gives a more precise estimation of average maximum expiratory velocity in both normal subjects and in patients with pulmonary disease.

The Nature of Pulmonary Ventilatory Insufficiency as Disclosed by an Indirect Measure of Velocity

Flow. *William F. Miller,* Robert L. Johnson, Jr.,* Nancy Wu* and Paul L. Richburg** (introduced by *Donald W. Seldin**). Department of Internal Medicine, Southwestern Medical School of the University of Texas, Dallas, and the Cardio-Respiratory Laboratory, Veterans Administration Hospital, McKinney, Texas.

To elucidate more precisely the nature of pulmonary ventilatory insufficiency a function test was devised which permits the identification and quantitative evaluation of various disturbances in pulmonary air flow and volume.

To estimate pulmonary air flow the 0.5, 0.75, and 1.0 second expiratory volumes (EV) were determined using a modified Gaensler-Collins Vitalometer. Pulmonary volume was estimated from the total vital capacity (TVC). These were compared with the maximum breathing capacity (MBC) in 100 normal subjects and 100 patients with pulmonary disorders.

In normal subjects the 0.5 second EV when expressed in liters per minute was only slightly higher than the MBC, but with a lower standard deviation. This close correlation does not hold true in diseased states where the MBC is an unreliable estimation of velocity air flow.

It was found more informative to plot the ratio $\frac{0.5 \text{ sec. EV}}{\text{TVC}} \times 100$ against the TVC expressed as % of predicted. This ratio was consistently 68.2 ± 4.9% in normal subjects (20–60 years, both sexes).

In evaluating the data a ratio >60% and a TVC >90% was considered normal. Pure restrictive ventilatory defects are represented by ratios >60% and TVC <90%. Pure obstructive defects produce ratios <60% and TVC >90%. Combined restrictive and obstructive defects are characterized by ratios <60% and TVC <90%.

This method provides a reliable expression of expiratory velocity as well as a measure of lung volume, thereby permitting precise definition of ventilatory defects during the course of pulmonary disease.

A Study of Pulmonary Vascular Resistance in Patients with Chronic Diffuse Pulmonary Emphysema During a 20-Minute Period of Breathing 100% Oxygen. *Russell H. Wilson.* Dallas, Texas and *Wayne Hoseth* and Mary E. Dempsey.** Minneapolis, Minnesota.

Twenty-one patients having severe pulmonary emphysema with oxygen unsaturation of the arterial blood had cardiac catheterization. The respiratory minute volumes, P_aCO_2, pH, and % oxygen saturation of the arterial blood were obtained while breathing room air and on completion of a 20-minute period of 100% oxygen breathing. All intracardiac pressures were measured before and during oxygen breathing. Pulmonary vascular resistance was calculated for both periods.

The t test of significance of the mean differences from zero while breathing room air and 100% oxygen was applied to the data: (1) the cardiac output decreased 0.5 L., $p < 0.05$, (2) the total pulmonary vascular resistance decreased 50.8 dynes sec./cm.$^{-5}$, $p < 0.01$, (3) the % oxygen saturation of arterial blood increased 11.6%, $p < 0.01$, (4) P_aCO_2 increased 12.9 mm. Hg, $p < 0.01$, (5) pH decreased 0.1, $p < 0.01$, (6) minute volume decreased 3 L. $p < 0.01$, (7) effective alveolar ventilation decreased 1.092 L./min., $p < 0.01$.

The correlation coefficients between these factors were: (1) the increase in % oxygen saturation and the decrease in pulmonary vascular resistance, $r = -0.7419$, $p < 0.01$, (2) the minute volume and the increase in P_aCO_2, $r = 0.1552$, $p > 0.5$, (3) the P_aCO_2 and the pH, $r = -0.7025$, $p < 0.01$, (4) the cardiac output and the decreased vascular resistance, $r = 0.1052$, $p > 0.05$, (5) the pH and the vascular resistance, $r = 0.0675$, $p > 0.5$, (6) the P_aCO_2 and the vascular resistance, $r = 0.4869$, $p < 0.01$, (7) the P_aCO_2 and effective alveolar ventilation, $r = 0.7161$, $p < 0.01$.

It was concluded that hypoxia caused an increase in pulmonary vascular resistance which was decreased by breathing 100% oxygen 20 minutes; however, the organic pulmonary vascular pathology caused the major rise in pulmonary arterial pressure. Upon removing the hypoxic stimulus to respiration, the respiratory minute volume, the effective alveolar ventilation, and the pH of arterial blood decreased; the P_aCO_2 increased. A temporary state of respiratory acidosis ensued. The close correlation between the rise in P_aCO_2 and the change in pulmonary vascular resistance may be an associated phenomenon rather than a cause and result relationship.

The Pathologic Physiologic Effects of Breathing 100% Oxygen and Respiratory Depressants in Hypoxic Patients with Pulmonary Emphysema having Compensated and Uncompensated Respiratory Acidosis. *Russell H. Wilson,* Dallas, Texas and *Mary Dempsey* and William T. McKenna,** Minneapolis, Minnesota.

Group 1. Twenty six patients with severe pulmonary emphysema were studied; all had increased residual volume and alveolar nitrogen retention above 2.5% after breathing oxygen for 7 minutes. Four of the group had terminal pulmonary emphysema. Right heart catheterization was done to obtain other data.

Group 2. Four patients with pulmonary emphysema and cor pulmonale had been given morphine gr. ⅙ before entering the hospital.

Group 3. Five additional patients with pulmonary emphysema were studied who had been given barbiturates while in the hospital.

The respiratory minute volumes, P_aCO_2, pH, and arterial oxygen % saturation were obtained 2

minutes before termination of the oxygen breathing in the first group of 26 patients.

Statistical analysis with the t test revealed: (1) the mean minute volume had decreased from 9.4 to 6.0 L. per minute, $p < 0.01$, (2) P_aCO_2 had increased from 48.7 to 62 mm. Hg, $p < 0.01$, (3) pH had decreased from 7.38 to 7.29, $p < 0.01$, (4) the % oxygen saturation had increased from 83.5 to 98.0, $p < 0.01$.

There was close correlation between the effective alveolar ventilation P_aCO_2 and pH, $p < 0.01$. The correlation between decrease in the minute volume, pH, and P_aCO_2 was not significant, $p > 0.5$.

Oxygen breathing with a decrease in the minute volume caused 4 patients with terminal emphysema to develop severe respiratory acidosis, confusion, disorientation and coma. Oxygen was discontinued and the patients reverted to the preoxygen status. Further oxygen breathing caused recurrence of uncompensated respiratory acidosis with coma.

Four patients with emphysema were given 1/6 gr. of morphine because they were thought to have left heart failure with anxiety. The respiratory minute volume and effective alveolar ventilation was decreased, leading to uncompensated acidosis. Five patients with severe emphysema were given 1.5 gr. of seconal because of insomnia. All developed severe respiratory acidosis. Following recovery from the effects of morphine and barbiturates, each group was allowed to breathe oxygen for 20 minutes. Respiratory acidosis recurred. Compensation or partial compensation occurred on recovery from the effects of either respiratory depressants or 100% oxygen.

It was concluded that patients with severe pulmonary emphysema should not receive 100% oxygen and/or respiratory depressants without caution because of the danger of increasing the severity of uncompensated respiratory acidosis.

Effect of Venesection on Pulmonary Function in Chronic Pulmonary Emphysema Complicated by Secondary Polycythemia. *J. Howland Auchincloss, Jr. and John Duggan.* Department of Medicine, Upstate Medical Center, State University of New York at Syracuse.

Six emphysematous polycythemic males were studied before and after removal of 1000–2500 cc. of blood. Only 1 patient presented evidence of right heart failure and all were stabilized as to symptoms and clinical findings. Before and after studies were completed within 10 days in 5 patients and 3 weeks in 1 patient. Other changes in therapy were avoided. Significant reductions in hematocrit and oxygen capacity were achieved in all patients.

Following venesection vital capacity increased in 2 patients, but maximum ventilatory capacity remained unchanged. In the 3 patients in whom lung volumes were determined total and functional residual capacities increased, but the ratio of residual volume to total capacity did not materially change, nor was there any evidence of improved intrapulmonary mixing of gases. In 2 of the 6 patient-the resting arterial oxygen saturation rose slightly, while pCO_2 was unchanged in all of 5 cases studied. Resting room air alveolo arterial gradients (4 cases) and dead space-tidal volume ratios (2 cases) were not altered. Two patients underwent the standard 30 step 1-minute exercise test. Both showed a higher exercise ventilation and a 5 and 9% increase in arterial oxygen saturation following venesection. In a second group of 4 patients it was found that removal of 500–1000 cc. of blood during right heart catheterization did not significantly raise the saturation of the mixed venous blood.

It is concluded that in the resting emphysematous polycythemic patient not in right heart failure the characteristic derangements in pulmonary function are not greatly modified by attempts to correct polycythemia. Further studies during exercise are indicated.

A Comparative Evaluation of the Effects of Intermittent Positive Pressure Breathing (IPPB) Alone, Nebulized Broncho-Dilators Alone, and IPPB Plus Nebulized Bronchodilators, in Patients with Chronic Bronchopulmonary Disease. *Nancy Wu,* William F. Miller,* Robert Cade,* Russel Horn* and Paul L. Richburg** (introduced by *Leonard L. Madison*). Department of Internal Medicine, Southwestern Medical School of the University of Texas, Dallas, and the Cardiorespiratory Laboratory, Veterans Administration Hospital, McKinney, Texas.

Studies designed to evaluate the beneficial effects of IPPB in pulmonary disease have been complicated by the simultaneous administration of bronchodilators. This investigation was undertaken in an effort to distinguish the effects of IPPB alone from those of the bronchodilators simultaneously administered, and to compare the effects of nebulized bronchodilators alone with those of nebulized bronchodilators administered by IPP.

Ventilatory function tests were performed on 24 patients with chronic bronchopulmonary disease before, 20 minutes after, and 1 hour after the following procedures: (1) Administration of IPPB alone (Bennett apparatus), (2) administration of nebulized bronchodilators by O_2 mask, and (3) administration of IPPB with nebulized bronchodilators.

IPPB alone produced no consistent change in the group as a whole. Although function improved in 5 patients with cor pulmonale, it decreased significantly in patients with asthma. In all patients, nebulized bronchodilator administration produced a significant improvement in dynamic

lung volumes and maximum breathing capacity. Furthermore, nebulized bronchodilator administered by IPPB produced an even greater and more prolonged improvement in function.

The decreased function resulting from IPPB alone in asthmatic subjects is probably due to reflex bronchospasm, whereas the improvement noted in patients with cor pulmonale suggests increased lung compliance.

It is concluded that IPPB alone is of no benefit in chronic bronchopulmonary disease but it enhances the effectiveness of simultaneously administered bronchodilators. This improved effectiveness may be due to improved distribution of the inhaled bronchodilator. The administration of nebulized bronchodilator by IPPB offers significant acute benefits over nebulized bronchodilator administered by O_2 mask.

Radioactive Iodine for Chronic Lung Disease. *Bernard A. Bercu and Harvey N. Mandell.* Department of Medicine, Washington University School of Medicine, Barnes Hospital, and the Washington University Unit I Medical Service, St. Louis City Hospital, St. Louis.

The present treatment for chronic pulmonary insufficiency is usually disappointing and frequently of only temporary benefit. Since one fundamental defect in chronic lung disease is a deficiency in the supply of oxygen to the body, it was thought worthwhile to determine the effect of lowering the basal requirements of the tissues for oxygen by making patients with chronic lung disease relatively hypothyroid.

Ten patients with pulmonary emphysema and/or fibrosis were selected. These patients had been treated repeatedly by the usual methods and were still markedly incapacitated either at rest or upon slight exertion. Since antithyroid treatment could not be expected to alter the fundamental pulmonary lesion, objective changes in lung function were not anticipated. In evaluating the effect of therapy, reliance was therefore placed upon standard exercise tolerance tests and upon subjective changes. Patients were considered significantly improved if they were able to perform activities which previously were intolerable because of dyspnea. Those who did not give evidence of increased exercise tolerance, even though they were improved subjectively, were considered as only questionably improved.

Of the 10 patients treated, 3 were initially made hypothyroid with tapazole. The other 7 were given I^{131} on 1 or more occasions. All patients were euthyroid prior to therapy. Seven patients were found to be significantly improved, 1 was questionably benefited, and 2 were unchanged. In 2 patients severe dyspnea developed after the tapazole was discontinued in preparation for the use of I^{131}. This dyspnea again disappeared in 1 patient after establishment of hypothyroidism. The other patient expired during the interval.

ROENTGENOLOGY

Combined Radioautographic and Histologic Studies Concerning the Radiation Effects of Colloidal Thorium Dioxide. *Abner Golden and Hermann J. Schaefer.** Department of Pathology, Emory University School of Medicine, Emory University, Georgia and Naval School of Aviation Medicine, U. S. Naval Air Station, Pensacola, Fla. (Supported by U. S. Navy Contract Nonr 73500.)

Delayed injurious effects of Thorotrast (colloidal thorium dioxide) when used in contrast radiography have been attributed to the prolonged presence in the body of radioactive material. Diffuse hepatic fibrosis has been described in man and experimental animals and a few observations suggest carcinogenicity. Thorotrast is frequently employed as a medium for cerebral angiography although it has been largely abandoned in hepatolienography.

Rabbits were given intravenous doses of Thorotrast ranging from 9 to 27 cc. and were sacrificed after periods of 1, 4, and 9 months. Hematologic studies indicated a tendency toward macrocytic anemia, although hemoglobin values changed only slightly. Histologic examination showed the accumulation of Thorotrast in progressively larger masses in reticuloendothelial cells, primarily in liver, spleen and bone marrow. No neoplasia or significant fibrosis was noted, although occasional disintegration of Thorotrast-laden cells was seen.

A radioautographic method was employed that permitted accurate localization of alpha emitting material in histologic preparations. Significant quantities of alpha radiation were present in some Thorotrast deposits. The alpha rays appeared to dissipate most of their energy within these deposits and, consequently, relatively little effective radiation reached the surrounding cells. Beta and gamma radiation from thorium is negligible. Therefore, it is concluded that whatever effects are produced in the body by Thorotrast are the result of physical properties other than radioactivity.

SURGERY

The Use of Chemically Sterilized Arterial Homografts: Experimental Clinical Observations. *D. Emerick Szilagyi, Paul R. Overhulse* and G. A. LoGrippo.* Departments of Surgery and Pathology, Henry Ford Hospital, Detroit.

A simple method of sterilizing effectively and harmlessly human arterial grafts obtained without aseptic precautions has long been sought, but with little success. On grounds of the experiences of Hartman and his associates in the sterilization of human plasma and of Lam and his associates in the sterilization of canine arterial transplants, the organic compound betapropiolactone (BPL), possessed of wide-range germicidal, sporicidal and virucidal qualities, seemed to us a most promising sterilizing agent for human arterial grafts.

Through series of parallel experiments on wet-preserved human arterial segments of varying dimensions the effects of BPL of graded concentrations have been studied on the histologic structure, tensile strength, bursting strength, elasticity and tissue-culture viability of the test specimens. It was found that in a concentration of 1.0% during a contact (by simple immersion) of 2 hours' duration BPL had no deleterious effects of importance on the graft characteristics investigated. During the past 4 months contaminated arterial homografts procured at routine autopsies and treated with betapropiolactone have been inserted in defects created by the following operations: resection of aortic bifurcation (2 cases), resection of external iliac artery (1 case), and resection of femoral artery (4 cases). During a period of observation ranging from 2 weeks to 4 months at this writing, all these grafts (from 8 to 25 cm. in length) have remained in excellent functional state by clinical or radiologic criteria. By analogy with observations in animal experiments of 2 years' duration (Lam et al), and on the basis of the findings of the laboratory studies enumerated, one has reason to expect that these short-term clinical results may stand the test of time.

The P/NPN Ratio as an Index of Muscle Damage during Post-traumatic Oliguria. *W. H. Meroney.* Department of Hepatic and Metabolic Diseases, Army Medical Service Graduate School, Washington, D. C.

Observations of 28 war casualties with oliguria revealed that plasma inorganic phosphate (P) rose earlier and to higher concentrations in patients with muscle necrosis than in patients with comparable damage to other tissues. Plasma nonprotein nitrogen (NPN), on the other hand, rose at a similar rate in all patients. Both P and NPN rose at rather regular rates, and graphs of the average P and the average NPN are superimposable.

After 4 days of oliguria the P of patients without muscle damage reached the level shown by the patients with muscle necrosis on day 2. P was related to time, as well as to muscle damage, whereas NPN was related only to time. A graph of P versus time is comparable with P versus NPN, and, therefore, the rate of rise of P can be expressed as P/NPN. Increasing P/NPN ratios were associated with increasing degrees of muscle damage, as assessed by clinicians unfamiliar with the chemical relationships under consideration. Seven patients without muscle damage had an average P/NPN ratio of .039; 6 patients with superficial muscle infection averaged .050; 5 patients with necrotizing myositis which was extirpated averaged .059; and 10 patients with uncontrollable necrotizing myositis averaged .071. The P/N ratio in muscle tissue is .068.

During post-traumatic oliguria an inordinate rise in P is indicative of muscle damage. If the exact duration of oliguria is unknown, it can be estimated from the NPN. The P/NPN ratio is an index of the degree of muscle damage.

Concerning the Selection of the Program

THE NUMBER OF ABSTRACTS submitted for the Annual Meeting has continued to increase. This year there were well over 150. The job of selecting a program has become increasingly difficult. This year each of the abstracts was reviewed by at least three men in different fields and many were evaluated by as many as six people. Although the bulk of the abstracts submitted came from the Northeast, it has been possible to achieve representation on the program from centers in the Central Atlantic, Southern, Midcontinental, and Western areas. Although the greatest number submitted dealt with metabolic, cardiovascular, and hematologic topics, the program includes presentations in the pulmonary, gastrointestinal, surgical, and neurologic fields. Although no claim is made that the best work was selected for presentation, it is hoped that the selections will provide an interesting and stimulating meeting.

STEWART WOLF
President, 1953–1954